(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 February 2003 (06.02.2003)

PCT

(10) International Publication Number
WO 03/010205 A1

(51) International Patent Classification[7]: C07K 21/04, 16/00, A61K 48/00, 39/395, C12N 15/00

(21) International Application Number: PCT/US02/23786

(22) International Filing Date: 26 July 2002 (26.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/307,600	26 July 2001 (26.07.2001)	US
10/201,642	24 July 2002 (24.07.2002)	US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*
before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/010205 A1

(54) Title: GENES INDUCED BY HYPOXIA

(57) Abstract: Solid tumors and other conditions related to angiogenesis, including wounds, bone fracture, follicular development, ischemia, retinopathy, psoriasis, and rheumatoid arthritis are treated or detected with reagents which either detect, promote, or disrupt expression of one or more of *HOG18, HOG3, HOG8, PLOD2, CA9, HXB, IGFBP5, STC1, HFARP, mig-6,* and *SSR4.* Each of these genes was found to be induced by hypoxia.

GENES INDUCED BY HYPOXIA

This application claims the benefit of provisional application serial no. 60/307,600 filed July 26, 2001, the content of which is expressly incorporated herein. The U.S. Government retains certain rights to this invention due to funding by the National Institutes of Health of NCI CGAP contract #S98-146.

FIELD OF THE INVENTION

The invention is related to methods for the enhancement or inhibition of the expression of genes related to responses to hypoxia. More specifically, the invention is related to methods to increase or decrease the expression of certain genes which promote angiogenesis, the growth of tumors, wound healing, the growth and development of tissues such as bone or ovarian follicles, and inflammatory conditions such as arthritis or psoriasis.

BACKGROUND OF THE INVENTION

Cellular responses to hypoxia have important effects on the development and metastasis of tumors, angiogenesis, wound healing, recovery from ischemia, and other physiological and pathological processes. Reduced oxygen availability can trigger a variety of cellular mechanisms including angiogenesis, cell-cycle arrest, apoptosis, and glycolysis.

The molecular mechanisms by which cells adapt to hypoxia are poorly understood. An initial response to hypoxia is increased levels of hypoxia-inducible factor 1 (HIF-1) protein (Semenza GL, J Appl Physiol 88:1474-80 (2000)). This transcription factor is a key regulator of hypoxia-driven apoptosis, growth arrest, and tumor

vascularization. HIF-1 is additionally linked to oncogenesis by the Von Hippel-Lindau tumor suppressor protein (vHL), which controls HIF-1 levels by proteolysis (Maxwell PH, et al., Nature 399:271-5 (1999)). Vascular endothelial growth factor (VEGF) is a powerful hypoxia-induced mitogen for endothelial cell growth, which plays a critical role in the development of tumor vessels (Yancopoulos GD, et al., Nature 407:242-8 (2000)). Expression of the angiopoietin family of secreted proteins is also regulated by hypoxia (Krikun G, et al. Biochem Biophys Res Commun 275:159-63 (2000)). During angiogenesis, the angiopoietins function with VEGF and Tie2, an endothelial-specific receptor with tyrosine kinase activity. Angiopoietin-1 (ANG1) is involved in recruitment of peri-endothelial cells by emerging blood vessels and in the maintenance of cell-cell and cell matrix association in mature capillaries. Angiopoietin-2 (ANG2) behaves as an antagonist to ANG1, thus blocking the Tie2 signal. The combination of ANG2 and VEGF causes disruption of cell-cell association, which promotes the differentiation phase of angiogenesis (Audero E, et al. Arterioscler Thromb Vasc Biol 21:536-41(2001); Yancopoulos GD, et al., Nature 407:242-8 (2000)).

Inhibition of angiogenesis is thought to provide an opportunity for therapy of cancer and other conditions involving responses to hypoxia. Normal tissues maintain a balance between cellular proliferation and oxygen supply. This balance is altered in solid tumors, resulting in focal regions with reduced oxygen levels compared to surrounding normal tissue (Thrall DE, et al., Radiother Oncol 44:171-6 (1997)). The cells in hypoxic regions either adapt to the hypoxic stress or die. Adaptation to a low oxygen environment can have serious consequences. For example, hypoxic tumor cells have a higher resistance to radiotherapy and certain chemotherapies (Brown JM, Cancer Res 59:5863-70 (1999)). Hypoxia can promote a higher mutation rate (Yuan J, et al., Cancer Res 60:4372-6 (2000)) and select for a more metastatic and malignant phenotype (Hockel

M, et al., Cancer Res 56:4509-15 (1996); Rofstad EK, Int J Radiat Biol 2000;76:589-605 (2000)). Tumor angiogenesis may be blocked by disrupting the expression of VEGF or its receptor (Schlaeppi JM, & Wood JM, Cancer Metastasis Rev 18:473-81 (1999)).

Angiogenesis can be either beneficial or problematic, depending upon the circumstances. In processes such as wound healing, bone healing, recovery from ischemia, and follicular development, angiogenesis provides beneficial increased vascularization. However, angiogenesis is problematic in disease states like retinopathy and conditions caused by inflammation such as rheumatoid arthritis and psoriasis. The ability to promote or inhibit angiogenesis provides a method for treating these disease states.

Thus, there is a need in the art for knowledge of genes whose expression is induced by hypoxia because the products of such genes modulate angiogenesis, tumor growth, and a variety of pathological conditions.

SUMMARY OF THE INVENTION

The inventors provide a series of methods for treating various diseases and conditions by employing reagents derived from genes whose expression is induced by hypoxia. In one embodiment, the invention provides a method of inhibiting angiogenesis associated with wound healing, retinopathy, ischemia, inflammation, microvasculopathy, bone healing, skin inflammation, or follicular development. An antisense polynucleotide comprising 15 or more consecutive nucleotides of the complement of a sequence selected from the group consisting of SEQ ID NO:1 (HOG3), SEQ ID NO:3 (HOG8), SEQ ID NO:5 (HOG18), SEQ ID NO:9 (CA9), SEQ ID NO:11 (HXB), SEQ ID NO:13 (IGFBP5), SEQ ID NO:15 (HFARP), SEQ ID NO:17(STC1), SEQ ID NO:19 (mig-6) and SEQ ID NO:21 (SSR4) is provided to a patient suffering from abnormalities of

wound healing, retinopathy, ischemia, inflammation, microvasculopathy, bone healing, skin inflammation, or follicular development, following which angiogenesis is inhibited in the patient.

In another embodiment, the invention provides another method of inhibiting angiogenesis associated with wound healing, retinopathy, ischemia, inflammation, microvasculopathy, bone healing, skin inflammation, or follicular development. An antibody which specifically binds to a polypeptide selected from the group consisting of SEQ ID NO:2 (HOG3), SEQ ID NO:4 (HOG8), SEQ ID NO:6 (HOG18), SEQ ID NO:10 (CA9), SEQ ID NO:12 (HXB), SEQ ID NO:14 (IGFBP5), SEQ ID NO:16 (HFARP), SEQ ID NO:18 (STC1), SEQ ID NO:20 (mig-6) and SEQ ID NO:22 (SSR4) is administered to the patient, following which angiogenesis is inhibited in the patient.

Still another embodiment of the invention provides a method of promoting angiogenesis associated with wound healing, retinopathy, ischemia, inflammation, microvasculopathy, bone healing, skin inflammation, or follicular development. A polypeptide selected from the group consisting of SEQ ID NO:2 (HOG3), SEQ ID NO:4 (HOG8), SEQ ID NO:6 (HOG18), SEQ ID NO:10 (CA9), SEQ ID NO:12 (HXB), SEQ ID NO:14 (IGFBP5), SEQ ID NO:16 (HFARP), SEQ ID NO:18 (STC1), SEQ ID NO:20 (mig-6) and SEQ ID NO:22 (SSR4) is administered to a patient, and angiogenesis is promoted in the patient.

Even another embodiment of the invention provides another method of promoting angiogenesis associated with wound healing, retinopathy, ischemia, inflammation, microvasculopathy, bone healing, skin inflammation, or follicular development. A vector comprising a nucleotide sequence encoding a polypeptide selected from the group consisting of SEQ ID NO:2 (HOG3), SEQ ID NO:4 (GOG8), SEQ ID NO:6 (HOG18), SEQ ID NO:10 (CA9), SEQ ID NO:12 (HXB), SEQ ID NO:14 (IGFBP5), SEQ ID

NO:16 (HFARP), SEQ ID NO:18 (STC1), SEQ ID NO:20 (mig-6) and SEQ ID NO:22 (SSR4) and a promotor is administered to a patient. The nucleotide sequence is operably linked to the promoter and is transcribed into a sense mRNA upon transcription of the vector, whereupon angiogenesis is promoted in the patient.

In another embodiment the invention provides a method of treating a tumor. An antisense polynucleotide comprising 15 or more consecutive nucleotides of the complement of a sequence selected from the group consisting of SEQ ID NO:1 (HOG3), SEQ ID NO:3 (HOG8), SEQ ID NO:5 (HOG18), SEQ ID NO:13 (IGFBP5), SEQ ID NO:15 (HFARP), SEQ ID NO:19 (mig-6) and SEQ ID NO:21 (SSR4) is administered to the patient and tumor growth is inhibited.

Yet another embodiment of the invention provides a method of treating a tumor, in which an antibody which specifically binds to a polypeptide selected from the group consisting of SEQ ID NO:2 (HOG3), SEQ ID NO:4 (HOG8), SEQ ID NO:6 (HOG18), SEQ ID NO:14 (IGFBP5), SEQ ID NO:16 (HFARP), SEQ ID NO:20 (mig-6) and SEQ ID NO:22 (SSR4) is admisistered to a patient. Tumor growth in the patient is inhibited.

Still another embodiment of the invention provides a method of diagnosing cancer in a subject. A polypeptide selected from the group consisting of SEQ ID NO:2 (HOG3), SEQ ID NO:4 (HOG8), SEQ ID NO:6 (HOG18), SEQ ID NO:14 (IGFBP5), SEQ ID NO:16 (HFARP), SEQ ID NO:20 (mig-6) and SEQ ID NO:22 (SSR4) is quantified in a test sample suspected of being neoplastic from the subject and in a non-neoplastic control sample. The quantity of the polypeptide in the test sample is compared with the quantity of the polypeptide in the non-neoplastic control sample. The subject is identified as having a cancer if the quantity of the protein is higher in the test sample than in the control sample.

Yet another embodiment of the invention provides a method of diagnosing cancer in a subject. An mRNA selected from the group consisting of SEQ ID NO:1 (HOG3), SEQ ID NO:3 (HOG8), SEQ ID NO:5 (HOG18), SEQ ID NO:13 (IGFBP5), SEQ ID NO:15 (HFARP), SEQ ID NO:19 (mig-6) and SEQ ID NO:21 (SSR4) is quantified in a test sample suspected of being neoplastic from the subject and in a non-neoplastic control sample. The quantity of the mRNA in the test sample is compared with the quantity of the mRNA in the non-neoplastic control sample. The subject is identified as having a cancer if the quantity of the protein is higher in the test sample than in the control sample.

Another embodiment provides a method of imaging a tumor. An antibody which specifically binds to a polypeptide selected from the group consisting of SEQ ID NO:2 (HOG3), SEQ ID NO:4 (HOG8), SEQ ID NO:6 (HOG18), SEQ ID NO:8 (PLOD2), SEQ ID NO:14 (IGFBP5), SEQ ID NO:16 (HFARP), SEQ ID NO:20 (mig-6) and SEQ ID NO:22 (SSR4) is administered to a subject or to a tissue sample from a subject. The antibody is covalently linked to a label. The label is detected and an image is formed of the distribution of the label in the subject or tissue sample.

BRIEF DESCRIPTION OF THE DRAWINGS

The application file contains at least one drawing executed in color. Copies of this patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

Figures 1A and 1B show the time course of expression of HOGs in 1.5% oxygen. In Fig. 1A cultured glioblastoma cells (D247-MG) were switched to 1.5% oxygen at zero hours and the levels of transcripts of the individual genes determined by real-time PCR to produce the time-course of the hypoxia response. In Fig. 1B the time course of CA9 protein expression was measured by western blot analysis of lysates from D247-MG cells

grown in atmospheric oxygen or 1.5% oxygen. Molecular weight markers are shown to the left.

Figures 2A and 2B show HOG induction by HIF-1 or hypoxia in malignant cells. In Fig. 2A D247-MG cells were transfected with *HIF-1α* and cultured at either atmospheric or 1% oxygen. Transcript levels are displayed relative to the same standard as determined by real-time PCR. Fig. 2B depicts HOG induction in malignant cell lines derived from commonly occurring cancers as determined by lowering the oxygen concentration from atmospheric to 1.5% oxygen and measuring induction by real-time PCR. The cell lines used were Normal Human Astrocytes (1); glioblastomas D263-MG (2), D392-MG (3), D502-MG (4), D566-MG (5) and U87 (6); medulloblastomas D283-Med (7), D341-Med (8), D425-Med (9), D556-Med (10), D581-Med (11) and UW228 (12); colon carcinomas SW480 (13) and HCT116 (14); non-small lung carcinoma NCI-H23 (15); and breast cancers SKBr3 (16) and MCF7 (17). Genes induced greater than 10-fold are displayed as 10-fold.

Figures 3A-3N show *in vivo* expression of *HOGs* in human solid tumors. Immunohistochemistry was used to co-localize CA9 (Fig. 3A, brown stain) and the chemical hypoxia ma rker, pimonidazole (Fig. B, green stain) in serial sections of an oropharyngeal squamous cell carcinoma, sccNij70. Regions staining red in B represents proliferating (IdUrd labeled) cells. A standard H & E stain of an adjacent section (Fig. 3C) was used to show necrotic cells (staining red). *In situ* hybridization for *NDRG1* transcript (Fig. 3E) shows co-localization with CA9 (Fig. 3D) and pimonidazole (Fig. 3F) in an oropharyngeal squamous cell carcinoma. Peri-necrotic staining in GBMs was observed for CA9 (Figs. 3G and 3J), *BNIP3* (Figs. 3H and 3K), *NDRG1* (Figs. 3I and 3L), *IGFBP3* (Fig. 3M) and HFARP (Fig. 3O). *IGFBP3* stains endothelial cells in addition to hypoxic regions not adjacent to vessels (Fig. 3N). Arrows point to necrotic

areas. Magnification was 10x for 3A to 3C, 3G to 3I and 3M; 25x for 3D to 3F, 3L and 3O; 50x for 3J and 3K; and 100x for 3N.

DETAILED DESCRIPTION OF THE INVENTION

The present inventors have discovered that the expression of certain genes is elevated in cells grown under hypoxic conditions. Specifically, the inventors discovered that expression of the genes *HOG18, HOG3, HOG8, PLOD2, CA9, HXB, IGFBP5, STC1, HFARP, mig-6*, and *SSR4* is increased under hypoxic conditions in human glioblastoma cells and several human tumors *in situ*. These and other hypoxia overexpressed genes (HOGs) can be used for the diagnosis and treatment of cancer and angiogenesis-related conditions. The practical applications of the discovery include the use of antisense polynucleotides and antibodies as antitumor agents, the use of antisense polynucleotides and antibodies to disrupt angiogenesis in pathological tissues, the use of polynucleotides or polypeptides to promote angiogenesis in wound healing or regeneration of tissues, and the use of oligonucleotide probes and antibodies as tumor markers in diagnosis and prognosis.

HOGs were identified based on Serial Analysis of Gene Expression (SAGE) (Velculescu VE, et al., Science 270:484-87 (1995)) of cells cultured under low oxygen conditions. Eleven genes (*HOG18, HOG3, HOG8, PLOD2, CA9, HXB, IGFBP5, STC1, HFARP, mig-6*, and *SSR4)* were identified whose expression previously was not known to be induced by hypoxia. Full-length cDNA sequences of these genes have been previously reported. The cDNA sequences for *HOG18, HOG3, HOG8, PLOD2, CA9, HXB, IGFBP5, STC1, HFARP, mig-6*, and *SSR4* are shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21, respectively, and the corresponding encoded amino acid sequences are shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22. No

function has been assigned previously to HOG18 (accession number NM_019058), HOG3 (accession number NM_017606), and HOG8 (accession number BC007832). Known functional properties of the remaining eight genes are summarized below.

The angiopoietin-related gene, *HFARP*, encodes a secreted protein reported to protect endothelial cells from apoptosis (Kim et al., Biochem J 346 Pt 3:603-610 (2000)).

Transcription of *mig-6* is induced by glucocorticoids, insulin, cAMP, retinoic acid vasoactive peptides, serum mitogen, diabetic nephropathy, and stress (Lee et al., Arch Biochem Biophys 269:106-113 (1989); Kent et al., Endocrinology 134:2237-2344 (1994); Wick et al. (Exp Cell Res 219(2):527-535 (1995); Makkinje et al., J Biol Chem 275:17838-47 (2000)). Transcription of *mig-6* is regulated during the cell cycle, with peak levels around mid G1 (Varley et al., Biochem Biophys Res Commun 254:728-733 (1999)).

The delta subunit of signal sequence receptor, also referred to as SSR4 or translocon-associated protein (TRAP) delta, spans the ER membrane once and has most of its mass at the lumenal side (Hartmann et al., Eur J Biochem 214(2):375-381 (1993)). The genomic and cDNA of human SSR4 has been isolated (Brenner et al., Genomics 44(1):8-14 (1997)).

CA9 is expressed in renal cell and cervical carcinomas and is being exploited for diagnostic (Uemura et al., Br J Cancer 81(4):741-746 (1999); Nogradi A, Am J Pathol 154:1-1 (1998); Vermylen et al., Eur Respir J 14(4):806-811 (1999); U.S. Patent No. 6,087,09) and therapeutic (Zavada et al, Br J Cancer 82(11):1808-1813 (2000)) U.S. Patent No. 5,387,676) purposes. *CA9* is regulated by vHL in renal cells through degradation of HIF-1α. CA9 is also increased by vHL mutations and shows peri-necrotic staining in various tumors (Ivanov et al., Proc Natl Acad Sci USA 95:12596-12601 (1998); Wykoff CC, et al. Cancer Res 60:7075-83 (2000)).

Hexabrachion (*HXB*) is an extracellular matrix glycoprotein which promotes endothelial cell sprouting with basic fibroblast growth factor (Schenk S, Mol Biol Cell 10:2933-43 (1999)). Expression of HXB is correlated with angiogenesis in breast cancer, gliomas, and lymphomas (Vacca A, et al., Leuk Lymphoma 22:473-81 (1996); Jallo GI, et al., Neurosurgery 41:1052-9 (1997); Tokes AM, et al., Pathol Res Pract 195:821-8 (1999)). Antibodies specific for HXB can inhibit angiogenesis (Canfield AE and Schor AM, J Cell Sci 108:797-809 (1995)) and anti-sense therapy halts vascular thickening of pulmonary arteries (Cowan KN, et al., J Clin Invest 105:21-34 (2000)). Bigner & Zalutsky (U.S. Patent No. 5,624,659) have described methods of treating brain tumors using radiolabeled monoclonal antibodies to HXB. Kimura (U.S. Patent No. 5,436,132) has demonstrated the quantitative determination of HXB by immunoassay in cerebrospinal fluid as a glioma marker.

PLOD2 is a lysyl hydroxylase which is involved in angiogenesis. Inhibitors of PLOD2 block collagen synthesis and promote the effectiveness of other compounds which inhibit angiogenesis (U.S. Patent No. 5,021,404). PLOD2 acts synergistically to inhibit angiogenesis when administered together with an angiostatic compound such as heparin or a heparin analogue (U.S. Patent No. 5,021,404). Several inhibitors of PLOD2 are known (U.S. Patent Nos. 5,328,913 and 4,797,471).

Ischemia produces an immediate decrease in expression of *IGFBP5* in neonatal rat brain (Clawson et al., Biol Signals Recept 8(4-5):281-293 (1999)). At longer times following an ischemic event, stimulation of IGFBP5 expression has been observed (Lee, et al. J Cereb Blood Flow Metab 16(2):227-236 (1996); Clawson et al., Biol Signals Recept 8(4-5):281-293 (1999)).

IGFBP5 and stanniocalcin (*STC1)* have been used as markers for vascular endothelial cells in tumors (St. Croix B, et al. Science 289:1197-202 (2000)). STC1 is

induced during endothelial cell differentiation in an *in vitro* model (Kahn J, et al. Am J Pathol 156:1887-900 (2000)). *STC1* mRNA is found in several cancer cell lines and tumor tissues, and the use of STC1 as a molecular marker for tumors has been suggested (Fujiwara et al., Int J Oncol 16:799-804 (2000); Miura W, et al., APMIS 108:367-372 (2000)).

Disrupting the expression of any one of *HOG3, HOG8, HOG18*, PLOD2, *HFARP, mig-6, CA9, HXB, SSR4, IGFBP5*, and *STC1* individually or in combination can be used to inhibit or treat angiogenesis-related conditions. Such conditions include retinopathy, microvasculopathy, inflammatory conditions such as rheumatoid arthritis, and skin inflammations like psoriasis. Antisense oligonucleotides or antisense polynucleotides that specifically bind to transcripts of these genes can be used to prevent their translation *in vivo*.

Oligonucleotides or polynucleotides based on the genes identified here can be delivered therapeutically to cells to inhibit angiogenesis. As defined herein, the terms "oligonucleotide" and "polynucleotide" are used interchangeably and either refers to two or more nucleotides linked covalently through phosphodiester bonds. Antisense constructs of *HOG3, HOG8, HOG18, PLOD2, HFARP, mig-6,CA9, HXB, SSR4, IGFBP5* or *STC1*, either alone or in combination, can be administered therapeutically to inhibit angiogenesis. Antisense constructs typically contain a promoter located 3' to and operably linked to the sequence encoding the desired antisense polynucleotide or antisense polynucleotide. Upon initiation of transcription at the promoter, an RNA molecule is transcribed which is complementary to the native mRNA molecule of the gene.

The polynucleotides of the present invention encode all or a portion of the polypeptides HOG3, HOG8, HOG18, PLOD2, HFARP, mig-6,CA9, HXB, SSR4,

IGFBP5 and STC1. These polynucleotides can be isolated and purified free from other nucleotide sequences by standard purification techniques, using restriction enzymes to isolate fragments comprising the coding sequences of interest. The polynucleotide molecules are preferably intron-free. Such cDNA molecules can be made *inter alia* by using reverse transcriptase with *HOG3, HOG8, HOG18, HFARP, mig-6,CA9, HXB, SSR4, IGFBP5* and *STC1* mRNA as a template. The polynucleotide molecules of the invention can also be made using the techniques of synthetic chemistry. The degeneracy of the genetic code permits alternate nucleotide sequences to be synthesized that will encode the desired amino acid sequence. All such nucleotide sequences are within the scope of the present invention. Degenerate nucleotide sequences encoding the polypeptides HOG3, HOG8, HOG18, PLOD2, HFARP, mig-6,CA9, HXB, SSR4, IGFBP5 and STC1, as well as homologous nucleotide sequences which are at least about 50, 55, 60, 65, 70, preferably about 75, 90, 96, or 98% identical to a nucleotide sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21 and the complements thereof also are within the scope of the present invention. Percent sequence identity between the sequences of two polynucleotides is determined using computer programs such as ALIGN which employ the FASTA algorithm, using an affine gap search with a gap open penalty of -12 and a gap extension penalty of -2. Complementary DNA (cDNA) molecules, species homologs, and variants of HOG3, HOG8, HOG18, PLOD2, HFARP, mig-6,CA9, HXB, SSR4, IGFBP5 and STC1 which encode polypeptides with comparable biological activity also are within the scope of the present invention. Polynucleotide molecules of the invention can be propagated in vectors and cell lines as is known in the art. The constructs may be on linear or circular molecules. They may be on autonomously replicating molecules or on molecules without replication sequences.

Any technique available in the art can be used to introduce genetic constructs into the cells. These include, but are not limited to, transfection with naked or encapsulated nucleic acids, cellular fusion, protoplast fusion, viral infection, and electroporation. Introduction of genetic constructs may be carried out *in vitro* or *in vivo*.

Antisense intervention in the expression of specific genes can also be achieved by the use of synthetic antisense polynucleotide sequences (*see* Lefebvre-d'Hellencourt et al, Eur Cytokine Net. 6:7 (1995); Agrawal, Tibtech, 14:376 (1996); Lev-Lehman et al, Antisense Oligomers in vitro and in vivo. In Antisense Therapeutics, A. Cohen and S. Smicek, eds (Plenum Press, New York) (1997)). Antisense polynucleotide sequences may be short sequences of DNA, typically at least 12, 15, 17, 20, 25, 30, 35, 40, 45, or 50 nucleotides in length, but may be as small as a 7-mer (Wagner et al, Nature Biotechnology 14:840-844 (1996)), designed to complement a target mRNA of interest and form an RNA:antisense duplex. This duplex formation can prevent processing, splicing, transport or translation of the relevant mRNA. An antisense compound hybridizes specifically when binding of the compound to the target RNA molecule interferes with the normal function of the target RNA and there is little or no measurable non-specific binding of the antisense compound to non-target sequences under conditions used for assays or *in vivo* therapeutic treatment.

When employed as pharmaceuticals, the antisense polynucleotides are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intraperitoneal, intravenous, intramuscular, and intranasal. Pharmaceutical compositions containing oligonucleotides of the invention are prepared in any manner well known in the pharmaceutical art and comprise at least one active compound. It is contemplated that the pharmaceutical composition can be administered directly into a tumor to be

treated. The compositions of the invention can be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing formulations known in the art.

Another method of delivery involves delivery of the naked antisense polynucleotides across the dermal layer. The delivery of naked antisense polynucleotides is well known in the art. See, for example, Felgner et al.,U.S. Pat. No. 5,580,859. It is contemplated that the antisense polynucleotides can be packaged in a lipid vesicle before delivery of the antisense polynucleotide.

An antisense polynucleotide or antisense construct is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. An effective amount is that amount which when administered alleviates the symptoms or inhibits tumor cell growth. Normal dosage amounts can vary from 0.1 to 100,000 micrograms, up to a total dose of about 1 g, depending upon the route of administration. The course of therapy may last minutes, hours, days, or up to several months or until diminution of the disease is achieved. Preferably the effective amount is from about 0.02 mg/kg body weight to about 20 mg/kg body weight. However, the amount of the antisense polynucleotide or antisense construct actually administered usually will be determined by a physician in light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

Antibodies or antigen-binding fragments that bind to any one of the polypeptides HOG3, HOG8, HOG18, PLOD2, HFARP, mig-6, CA9, HXB, SSR4, IGFBP5, or STC1 can be used individually or in combination to inhibit angiogenesis. Antibodies or

antigen-binding fragments bind specifically to these gene products preventing physiological action of the polypeptides.

Antibodies directed against the polypeptides of this invention are immunoglobulins (*e.g.*, IgG, IgA, IgM, IgD, or IgE) or portions thereof that are immunologically reactive with the polypeptide of the present invention. As used herein, the term "antibody" includes whole immunoglobulin molecules, fragments of immunoglobulin molecules, and modified or synthetic immunoglobulins. The term "antibody" also includes single-chain antibodies, which generally consist of a variable domain of a heavy chain linked to a variable domain of a light chain. The production of single-chain antibodies is well known in the art (*see, e.g.*, U.S. Pat. No. 5,359,046). An antibody of this invention may also be a humanized antibody, which refers to a molecule that has its antigen-binding regions derived from a non-human species immunoglobulin and the remainder of the antibody molecule derived mainly from a human immunoglobulin antibodies which are known in the art (*see, e.g.* U.S. Pat. Nos. 5,777,085 and 5,789,554). It can be a molecule that has multiple binding specificities, such as a bifunctional antibody. Bifunctional antibodies can be prepared by any technique known to those of skill in the art, including the production of hybrid hybridomas, disulfide exchange, chemical cross-linking, addition of peptide linkers between two monoclonal antibodies, the introduction of two sets of immunoglobulin heavy and light chains into a particular cell line, and so forth. Alternatively, peptides corresponding to specific regions of the polypeptide encoded by the target gene may be synthesized and used to create immunological reagents according to well known methods.

Antibodies directed against a polypeptide encoded by a target gene may be generated by immunization of a mammalian host, including a rat, rabbit, goat, sheep, horse, pig, or primate. Such antibodies may be polyclonal or monoclonal. Preferably

they are monoclonal. Methods to produce polyclonal and monoclonal antibodies are well known to those of skill in the art. For a review of such methods, see Harlow & Lane (1988) Antibodies, A Laboratory Manual; Yelton, et al., Ann. Rev. of Biochem. 50:657-80 (1981); and Ausubel, et al., Current Protocols in Molecular Biology, John Wiley & Sons, (1989)). Determination of immunoreactivity with a polypeptide encoded by a target gene may be made by any of several methods well known in the art, including by immunoblot assay and ELISA. Monoclonal antibodies with affinities of 10^{-8} M^{-1} or preferably 10^{-9} to 10^{-10} M^{-1} or stronger are considered specific to a given protein and are typically made by standard procedures as described, *e.g.*, in Harlow & Lane, 1988.

Additionally, one of skill in the art has a variety of methods available which may be used to alter the biological properties of the antibodies of this invention. Such methods include chemical alteration, addition of buffer components, or amino acid substitutions which can increase or decrease the stability or half-life, immunogenicity, toxicity, affinity, or yield of a given antibody molecule.

Angiogenesis can also be inhibited by decreasing translation of mRNA by reducing the amount of available mRNA through the use of ribozymes that are capable of cleaving mRNA expressed by *HOG3*, *HOG8*, *HOG18*, *PLOD2, HFARP*, *mig-6*, *CA9*, *HXB*, *SSR4*, *IGFBP5*, and *STC1*. Ribozymes can be administered directly or as a ribozyme-expressing construct. The primary sequence of the target gene can be used to design ribozymes that can target and cleave specific essential gene sequences. There are a number of different types of ribozymes. Most synthetic ribozymes are generally hammerhead, *Tetrahymena,* and hairpin ribozymes. Methods of designing and using ribozymes to cleave specific RNA species are known in the art, see Zhao, et al., Mol Cell Neurosci 11:92-97(1998); Lavrovsky et al. (1997); and Eckstein "Exogenous Application of Ribozymes for Inhibiting Gene Expression", in *Oligonucleotides as Therapeutic*

Agents, Ciba Foundation Symposium 209, John Wiley & Sons, Chichester, England, pp. 207-217 (1997)).

It is sometimes desirable to promote angiogenesis, for example, to aid in wound healing, bone healing, follicular development, tissue regeneration following ischemia, or other conditions in which increased blood flow to a tissue or organ is desirable. Increased vascularization results in increased blood flow, which aids in healing and developing damaged tissues. Angiogenesis can be promoted by administering any one of the polypepetides HOG3, HOG8, HOG18, PLOD2, HFARP, CA9, HXB, mig-6, SSR4, IGFBP5, or STC1, individually or in combination. Methods of polypeptide expression, purification, and formulation are well-known in the art and any may be used without limitation.

It is also possible to increase expression of *HOG3, HOG8, HOG18, PLOD2, HFARP, CA9, HXB, mig-6, SSR4, IGFBP5,* or *STC1* by administering a vector comprising at least seven nucleotides that encode any part or all of one or more of the genes *HOG3, HOG8, HOG18, PLOD2, HFARP, CA9, HXB, mig-6, SSR4, IGFBP5,* or *STC1* operably linked to a promoter. Expression of sense mRNA molecules encoding HOG3, HOG8, HOG18, HFARP, mig-6,CA9, HXB, SSR4, IGFBP5 or STC1 polypeptides promotes angiogenesis. Methods for obtaining the polynucleotides required for this embodiment are well-known in the art.

Disrupting the expression of any one of *HOG3*, *HOG8*, *HOG18*, *PLOD2*, *HFARP*, *mig-6*, *SSR4*, and *IGFBP5* individually or in combination can be used to treat tumors. These genes are important in vascularization of tumors, because vascularization allows tumors to increase in size and to undergo metastasis. Antisense polynucleotides or oligonucleotides targeted to these genes can be used to prevent translation *in vivo*, which can prevent angiogenesis and stop or reduce tumor growth. Gene therapy to increase

expression of angiostatin, an inhibitor of angiogenesis, was recently demonstrated to inhibit the growth of tumors in mice (Matsumoto et al., Oral Oncol 37:369-78 (2001)), thereby establishing the feasibility of blocking tumor growth by introducing genes which inhibit angiogenesis. Production and use of antisense polynucleotides is known in the art and was discussed previously. Antibodies or antigen-binding fragments that bind to one of the polypeptides HOG3, HOG8, HOG18, HFARP, mig-6, SSR4, or IGFBP5 can also be used individually or in combination to treat tumors.

Quantifying gene expression of *HOG3*, *HOG8*, *HOG18*, *HFARP*, *mig-6*, *PLOD2*, *SSR4*, or *IGFBP5*, either singly or in combination, can be used to diagnose cancer in a subject. Expression of *HOG3*, *HOG8*, *HOG18*, *HFARP*, *mig-6*, *PLOD2*, *SSR4*, or *IGFBP5* in a test sample suspected of being cancerous can be compared to the expression of the same gene or genes in a second sample from a normal subject. Increased expression of at least one gene in the test sample relative to the normal sample identifies the test sample as potentially cancerous. Any method for observing gene expression can be used, without limitation. Common methods are quantification of expressed mRNA, *e.g.*, by Northern blot analysis or other hybridization techniques, or quantification of expressed polypeptides by SDS-PAGE, Western blot, or immunoassay.

For gene therapy purposes, cells can be transfected *in vitro* and administered to a subject. Alternatively, cells can be directly transfected *in vivo*. Delivery of nucleic acid molecules can be accomplished by any means known in the art. Gene delivery vehicles are available for delivery of polynucleotides to a cell, a tissue, an organ, or a mammal for expression. For example, a polynucleotide or oligonucleotide of the invention can be administered either locally or systemically in a gene delivery vehicle. Gene delivery constructs can contain viral or non-viral vectors in either *in vivo* or *ex vivo* modality. Expression of the gene of interest can be driven by endogenous mammalian or

heterologous promoters. Expression of the coding sequence *in vivo* can be either constitutive or regulated. The invention includes gene delivery vehicles capable of expressing the contemplated polynucleotides. The gene delivery vehicle is preferably a viral vector and, more preferably, a retroviral, adenoviral, adeno-associated viral, herpes viral, or alphaviral vector. The viral vector can also be an astroviral, coronaviral, orthomyxoviral, papovaviral, paramyxoviral, parvoviral, picornaviral, poxviral, togaviral vector. *See generally*, Jolly, Cancer Gene Therapy 1:51-64 (1994); Kimura, Human Gene Therapy 5:845-852 (1994), Connelly, Human Gene Therapy 6:185-193 (1995), and Kaplitt, Nature Genetics 6:148-153 (1994).

Delivery of the gene therapy constructs of this invention into cells is not limited to the above mentioned viral vectors. Other delivery methods may be employed such as, for example, nucleic acid expression vectors; polycationic condensed DNA (*see* Curiel, Hum Gene Ther 3:147-154 (1992); ligand linked DNA (*see* Wu, J. Biol. Chem. 264:16985-16987 (1989)); eucaryotic cell delivery vehicles (*see* U.S. Pat. No. 6,015,686); deposition of photopolymerized hydrogel materials; hand-held gene transfer particle gun (U.S. Pat. No. 5,149,655); ionizing radiation (U.S. Pat. No. 5,206,152 and WO 92/11033); nucleic charge neutralization; or fusion with cell membranes. Additional approaches are described in Philip, Mol. Cell. Biol. 14:2411-2418 (1994) and in Woffendin, Proc. Natl. Acad. Sci. 91:1581-585 (1994). The sequence can be inserted into a vector containing control sequences for high level expression. The vector can be incubated with synthetic gene transfer molecules including polymeric DNA-binding cations like polylysine, protamine, or albumin. A DNA-binding molecule can in turn be linked, preferably covalently, to a cell targeting ligand which binds specifically to a desired cell surface receptor expressed on a target cell. Targeting ligands include, for example, asialoorosomucoid (Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)); insulin

(Hucked, Biochem. Pharmacol. 40:253-263 (1990)); galactose (Plank, Bioconjugate Chem 3:533-539 (1992)); lactose; and transferrin. Naked DNA may also be employed. Exemplary naked DNA introduction methods are described in PCT Patent Publication No. WO 90/11092 and U.S. Pat. No. 5,580,859. Uptake efficiency may be improved using biodegradable latex beads which are efficiently transported into cells after endocytosis. The method may be improved further by treatment of the beads to increase hydrophobicity and thereby facilitate disruption of the endosome and release of the DNA into the cytoplasm. Liposomes, that can act as gene delivery vehicles are described in U.S. Pat. No. 5,422,120, PCT Patent Publication Nos. WO 95/13796, WO 94/23697, and WO 91/144445, and EP No. 524,968.

The pharmaceutical compositions of this invention may be administered using microspheres, microparticulate delivery systems, or other sustained release formulations. Sustained release formulations can be placed in, near, or otherwise in communication with affected tissues or the bloodstream.

The methods of this invention also may be accomplished using liposomes, which can optionally contain other agents to aid in targeting or administration of the compositions to the desired treatment site. Liposomes containing compositions contemplated for use with methods of the invention may be prepared by well-known methods (See, e.g. DE 3,218,121; Epstein et al. (1985) Proc. Natl. Acad. Sci. U.S.A. 82:3688-92; Hwang et al. (1980) Proc. Natl. Acad. Sci. U.S.A. 77:4030-34; U.S. Pat. Nos. 4,485,045 and 4,544,545).

Effective doses of the pharmaceutical compositions of the present invention will vary depending upon many different factors, including the form of the composition administered, the means of administration, target site, physiological state of the patient, antibody affinity, and other medicments administered. Thus, treatment dosages will need

to be titrated to optimize safety and efficacy; such can be readily determined and are routine to the ordinarily skilled artisan. In determining the effective amount of polypeptide or polynucleotide to be administered, the physician evaluates, for example, the particular composition used, the disease state being diagnosed; the age, weight, and condition of the patient, formulation toxicities, disease progression, etc. The dose will also be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular formulation. Doses ranging from about 10 ng to 1 g polypeptide per patient are typical. Doses generally range between about 0.01 and about 50 mg polypeptide per kilogram of body weight; preferably between about 0.1 and about 5 mg/kg polypeptide of body weight.

Oligonucleotide probes and antibodies can be used as tumor markers in diagnosis and prognosis of cancer. The expression product monitored may be RNA or protein. Multiple expression products, *e.g.*, 2, 3, 4, 5, 7, 10, 15, 20, 30, 50, 100, 300, 500, or 1000 or more expression products can be quantified simultaneously. Methods of monitoring gene expression are well known in the art and any may be used. For example, RNA levels can be measured by Northern blotting and other hybridization techniques, nuclease protection, microarrays, RT-PCR, and differential display. The term quantifying when used in the context of quantifying transcription levels of a gene can refer to absolute or to relative quantification. Absolute quantification may be accomplished by inclusion of known concentration(s) of one or more control target nucleic acids and referencing the hybridization intensity of unknowns with the known target nucleic acids, *e.g.*, through generation of a standard curve. Alternatively, relative quantification can be accomplished by comparison of hybridization signals between a sample derived from a test subject and a sample derived from a normal subject to determine differences in hybridization intensity and, by implication, transcription level.

One of skill in the art can readily determine differences in the amount of gene expression product from the test sample as compared to a normal subject using, *e.g.*, Northern blots and nucleotide probes. The quantity of mRNA expressed from at least one of HOG3, HOG8, HOG18, HFARP, mig-6, PLOD2, SSR4, or IGFBP5 in a test sample of a human suspected of having cancer, can be compared with the mRNA expression from at least one of HOG3, HOG8, HOG18, HFARP, mig-6, PLOD2, SSR4, and IGFBP5 in a normal sample. This can be done, for example, using *in situ* hybridization in tissue section or in Northern blots containing mRNA. A higher level of mRNA expressed from a gene represented by a HOG3, HOG8, HOG18, HFARP, mig-6, PLOD2, SSR4, and IGFBP5 polynucleotide in the test sample as compared to the normal sample is indicative or suggestive of cancer in the suspect human who has provided the test sample. Preferably, the increased level of mRNA expressed from a *HOG3, HOG8, HOG18, HFARP, mig-6, PLOD2, SSR4,* or *IGFBP5* gene in the test sample is at least 25%, 50%, 100%, 150%, 200%, or 250% higher than in the normal body sample.

To facilitate detection any polynucleotide or oligonucleotide of this invention can be labeled using standard methods. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. For example, polynucleotides or oligonucleotides can be radiolabeled with ^{32}P or covalently linked to a fluorescent or biotinylated molecule. Other techniques such as high density DNA array hybridization, ribonuclease protection assay, and serial analysis of gene expression can also be used. Oligonucleotide probes specific to the nucleotides encoded by *HOG3, HOG8, HOG18, HFARP, mig-6, PLOD2, SSR4,* and *IGFBP5* can be generated using the polynucleotide sequences of *HOG3, HOG8, HOG18, HFARP, mig-6, PLOD2, SSR4,* and *IGFBP5* genes. The probes are preferably at least 12, 14, 16, 18, 20, 22, 24, or 25 nucleotides in length and can be less than 2, 1, 0.5, 0.1, or 0.05 kb in length.

The probes can be, for example, synthesized chemically, generated from longer polynucleotides using restriction enzymes, or amplified enzymatically. The probes can be labeled, for example, with a radioactive, biotinylated, or fluorescent tag. A mixture of probes can also be used. Such mixture can contain a plurality of probes which are specific to different genes identified in this invention so that the expression of one or more genes can be monitored simultaneously. Alternatively, each of a plurality of probes can be used separately.

The antibodies of the present invention can be used to detect any one of HOG3, HOG8, HOG18, HFARP, mig-6, PLOD2, SSR4, and IGFBP5 in histological sections of glioma tissue as well as in other solid tumors, such as breast cancer and lung cancer. Tissue samples are preferably permeabilized with a sufficient amount of a suitable detergent to release membrane proteins into solution prior to immunological detection. One can detect antibody binding to extracts of tissue samples by any detection means known in the art, for example, radioimmunoassay, enzyme-linked immunoadsorbent assay, complement fixation, nephelometric assay, immunodiffusion, or immunoelectrophoretic assay. Alternatively, the antibodies can be used as an immunohistochemical reagents to visualize HOG3, HOG8, HOG18, HFARP, mig-6, PLOD2, SSR4, and IGFBP5 polypeptides in tissue sections.

A particularly useful stain for use in enzyme-linked antibody assays employs peroxidase, hydrogen peroxide and a chromogenic substance such as aminoethyl carbazole. The peroxidase (a well known enzyme available from many sources) can be coupled to an antibody specific for one of HOG3, HOG8, HOG18, HFARP, mig-6, PLOD2, SSR4, or IGFBP5 or merely complexed to it via one or more antibodies. For example, a goat anti-peroxidase antibody and a goat antibody specific for one of HOG3, HOG8, HOG18, HFARP, mig-6, PLOD2, SSR4, and IGFBP5 can be complexed via an

anti-goat IgG. Such techniques are well known in the art. Other chromogenic substances and enzymes may also be used.

The antibodies of the invention can be administered to a patient or to a tissue sample from a patient for locating a tumor or imaging analysis or a tumor. For such purposes, the antibodies are typically conjugated to an imaging agent, such as ^{123}I, ^{131}I, or ^{111}In. Alternatively, ^{13}C-enriched antibodies can also used in combination with magnetic resonance imaging. For in vitro analysis of tissue samples from a patient, a variety of imaging agents and techniques are known in the art. For example, the imaging agent can be a colored or fluorescent dye or an enzyme yielding a colored or fluorescent product. Methods of conjugation and production of isotopically enriched antibodies are routine and well known in the art. A diagnostically effective amount of antibody is one which allows the observer to distinguish between normal tissues and those containing elevated levels of HOG3, HOG8, HOG18, HFARP, mig-6, PLOD2, SSR4, or IGFBP5. Determination of such amounts is within the skill of the art. Methods of imaging or detecting the bound antibodies in a patient or in a tissue sample from a patient are also known in the art. For example, the patient may be scanned for radiation emitted by the imaging agent or a tissue section stained with the labeled antibody may be observed using a microscope.

The compounds of this invention can also be utilized in radioimmuno- or radiation therapy. This process differs from the corresponding diagnostic techniques only in the quantity and type of isotope employed. The objective is the destruction of tumor cells by high-energy shortwave radiation with a minimum range. Suitable ß-emitting ions are, for example, ^{46}Sc, ^{47}Sc, ^{48}Sc, ^{72}Ga, ^{73}Ga and ^{90}Y. Suitable α-emitting ions exhibiting short half-life periods are, for example, ^{211}Bi, ^{212}Bi, ^{213}Bi and ^{214}Bi. A suitable

nuclide emitting photons and electrons is ^{158}Gd which can be obtained from ^{157}Gd by neutron capture.

All references and patents cited herein are incorporated by reference in their entirety.

The following examples are provided by way of illustration and are not intended to limit the scope of the invention in any way.

EXAMPLES

Example 1. Comparison of gene expression in normal and hypoxic human glioblastoma cells

One application of the present invention involves quantitative comparison of gene expression in normal and tumor cells. RNA expression levels of *HOG3*, *HOG8*, *HOG18*, *HFARP*, *mig-6*, *PLOD2*, *SSR4*, and *IGFBP5* were compared in normal and hypoxic human glioblastoma cells.

Cells were grown using standard cell culture techniques either in equilibrium with atmospheric oxygen or using 1.5% oxygen, approximating tumor hypoxia levels. Real-time PCR from a cDNA template was performed using a thermocycler with continuous fluorescent monitoring capabilities (LightCycler™, Roche Diagnostics) and SYBR Green I (Molecular Probes, Eugene, OR) to analyze the kinetics of PCR product accumulation. PCR conditions and data analysis were reproduced as described (Loging WT, et al., Genome Res 10:1393-402 (2000)) except 0.5 μM PCR primer and 500 μM of each dNTP was used. Primers specific for a 221-bp segment of *β-actin* were used to confirm cDNA integrity and normalization of cDNA yields. Primers specific for each hypoxia-inducible gene were designed with 140- to 240-bp products (all primer sequences available upon

request). Relative expression levels were determined in duplicate by comparison to a serially diluted standard using the thermocycler software.

Measurement of transcript levels using real-time PCR and SAGE analysis showed that expression of *HOG3*, *HOG8*, *HOG18*, *HFARP*, *mig-6*, *PLOD2*, *SSR4*, and *IGFBP5* in hypoxic glioblastoma cells was increased between 2- and 12-fold as compared to cells grown under normal aerobic conditions (Table 1).

Table 1. Genes induced by hypoxia in glioblastoma cell line, D247-MG

SAGE Tag[e]	Gene Symbol[a] (Name)	Accession[b]	Fold Inc[c] SAGE	Fold Inc[c] PCR
TTTGTTAAAA	*HOG18** (hypothetical protein FLJ20500)	NM_019058	10x	5.7x
GCCACGTTGT	*HOG3** (hypothetical protein DKFZp434K1210)	NM_017606	9x	4.0x
GTGCTGGTGC	*HFARP** or *PGAR** (Hepatic fibrinogen/angiopoietin-related protein, PPAR-γ angiopoietin-related protein)	NM_016109	8x	12x
CAGCCAAATA	*HOG8** (similar to F-box only protein 6, a receptor for ubiquitination targets)	BC007832	8x	2.1x
CTTAAGAAAA	*mig-6** (Mitogen-inducible gene 6)	AL137274	7x	2.5x
TGTTAGAAAA	*PLOD2* (Lysine hydroxylase 2)	NM_000935	5x	4.4x
GATAGCACAG	*IGFBP5* (Insulin-like growth factor binding protein 5)	L27560	4x	4.6x
GCTCTCTATG	*SSR4* (Translocon associated protein delta)	NM_006280	3x	2.3x

[a]HUGO gene symbols are provided, or marked (*) if not yet available. Genes already known to be hypoxia are referenced.
[b]GenBank or RefSeq accession number corresponding to the SAGE tag.
[c]Fold increases (Fold Inc) are the ratio of hypoxic to normal transcript levels for SAGE and real-time PCR.
[d]Not Tested.
[e]SEQ ID NOS:23-30, respectively.

Example 2. Time course of gene induction by hypoxia

A time course of induction was performed on 12 hypoxia-inducible genes using real-time PCR (Fig. 1A). These genes all had a time course similar to *VEGF*, except for *CA9, NDRG1, HFARP and HOG18*, which were induced to a higher fold induction. Most of the genes required a 12-hour exposure prior to significant induction, implying an adaptation to chronic, rather than acute, hypoxia. Western blotting using an antibody to CA9 showed that protein levels increased with a time course similar to that of transcript levels (Fig. 1B).

Example 3. Regulation of hypoxia-induced genes by HIF-1

HOG18, *HOG3*, *HFARP*, *CA9*, *IGFBP5* and *IGFBP3* were tested to see if these genes might be regulated by HIF-1. *VEGF*, an HIF-1 regulated gene, was used as a positive control (Ravi R, et al., Genes Dev 14:34-44 (2000)). Standard transient transfection was able to insert *HIF-1α* subunit gene plasmid (or a lac-Z control plasmid) into about 20% of the D247-MG cells as demonstrated by β-galactosidase staining. All of the above genes showed a reproducible increase in expression due to *HIF-1α* at both atmospheric and 1% oxygen (Fig. 2A).

Example 4. Hypoxia-induced gene expression in malignant cell lines.

HOG induction in malignant cell lines derived from commonly occurring cancers was determined by lowering the oxygen concentration from normal to 1.5% oxygen and measuring induction by real-time PCR. The 17 cell lines used were Normal Human Astrocytes (1), glioblastomas D263-MG (2), D392-MG (3), D502-MG (4), D566-MG (5) and U87 (6), medulloblastomas D283-Med (7), D341-Med (8), D425-Med (9), D556-Med (10), D581-Med (11) and UW228 (12), colon carcinomas SW480 (13) and HCT116 (14), non-small lung carcinomas NCI-H23 (15) and breast cancers SKBr3 (16) and MCF7 (17). Genes induced greater than 10-fold are displayed as 10-fold. The results are displayed in (Fig. 2B).

Example 5. *In vivo* studies of hypoxia-induced genes.

The *in vivo* response to hypoxic conditions in human solid tumors was examined. Pimonidazole, a bioreductive marker (Raleigh JA et al., Cancer Res 58:3765-8 (1998), was used to accurately mark the hypoxic cells (Wijffels KI, et al., Br J Cancer 83:674-83 (2000)) of cervical or head and neck tumors. Staining of adjacent frozen sections

allowed determination of HOG expression co-localized with pimonidazole and other markers. Oropharynx carcinoma biopsies that were previously labeled with pimonidazole hydrochloride (Hypoxyprobe-1, Natural Pharmacia International Inc) and iododeoxyuridine (IdUrd), an S-phase marker, were obtained during diagnostic examination under anesthesia. Pimonidazole and IdUrd were injected intravenously, 2 h and 20 min, respectively, before biopsy as previously described (Wijffels KI et al., Br J Cancer 83:674-83 (2000)).

Immunohistochemical staining for CA9 was performed on 5-8 μm fresh frozen tissue sections using mouse monoclonal antibodies to the target hypoxia induced protein at a dilution of 3.2 mg/ml. The slides were fixed with acetone, blocked with horse serum, and sequentially incubated at room temperature with primary antibody, biotinylated secondary antibody, and avidin-biotin horseradish peroxidase complexes. Bound antibody was detected using 3,3'-diaminobenzidine and hydrogen peroxide, counterstained with 1% hematoxylin, and permanently mounted.

For visualization of pimonidazole and IdUrd, 5 μm sections were placed in pre-cooled acetone at 4°C for 10 min, air-dried and rehydrated with PBS. Tissue DNA was denaturated in 2N HCl for 10 min. To neutralize pH, sections were rinsed in 0.1M Borax followed by rinsing in PBS. Sections were incubated for 45 min at 37°C with 1 μg/ml anti-IdUrd and rabbit-anti-pimonidazole 1:200 in polyclonal liquid diluent. Next, sections were incubated for 90 min at room temperature in goat-anti-rabbit-ALEXAFLUOR488 (Molecular Probes, Eugene, OR) and goat-anti-mouseCy3, both 1 μg/ml in polyclonal liquid diluent. Between incubations the sections were rinsed in PBS and finally mounted with Fluorostab.

Non-radioactive *in situ* hybridization was performed using digoxigenin-labeled antisense RNA probes. PCR was used to generate 350- to 600- bp products specific to

each HOG and these products were subcloned into a pBluescript KS- (Stratagene). After growth in *E. coli*, the plasmid was cut at a unique poly-linker site to create a linear probe. Digoxigenin-labeled RNA probes, from both the sense and antisense strands, were generated using the digoxigenin RNA labeling reagents and either T7 or T3 polymerase (Roche Diagnostics). Alternatively, the T7 promoter was incorporated into an antisense primer and the RNA probes were generated as described earlier (St. Croix B, et al., Science 289:1197-202 (2000)). Fresh frozen sections are cut to 8 μm for *in situ* hybridization and processed as previously described (St. Croix B, et al., Science 289:1197-202 (2000)).

Example 6. Diagnosis and localization of a tumor in a patient.

Monoclonal antibodies to one of HOG3, HOG8, HOG18, HFARP, mig-6, PLOD2, SSR4, or IGFBP5 are coupled to ^{111}In via via N-succinimidyl-3-(tri-n-butylstanyl)benzoate (*see, e.g.*, Zalutsky M and Narula A, Appl. Radiat. Isot. 38:1051 (1987). A pharmaceutical formulation of the labeled antibody is prepared in sterile pyrogen-free phosphate-buffered saline solution and administered intravenously to the subject. The tumor is localized using a gamma ray detector sensitive to ^{111}In emissions.

Example 7. Treatment of a patient with a brain tumor.

A subject found to have increased quantities of HOG3, HOG8, HOG18, HFARP, mig-6, PLOD2, SSR4, and IGFBP5 and having a solid tumor residing in the cerebral cortex is treated using therapeutic monoclonal antibodies that bind specifically to one of these proteins. The antibody is coupled to ^{131}I via N-succinimidyl-3-(tri-n-butylstanyl)benzoate (*see, e.g.*, Zalutsky M and Narula A, Appl. Radiat. Isot. 38:1051 (1987)) to form a therapeutic monoclonal antibody. The therapeutic monoclonal

antibody is provided in a pharmaceutical formulation of sterile pyrogen-free phosphate-buffered saline solution and administered via intrathecal injection into the carotid artery. The patient receives 300 mCi of therapeutic antibody. The antibody is administered to the subject in a series of regular, periodic administrations.

CLAIMS

We claim:

1. A method of inhibiting angiogenesis associated with wound healing, retinopathy, ischemia, inflammation, microvasculopathy, bone healing, skin inflammation, or follicular development, comprising:

providing to a subject in need thereof an antisense polynucleotide comprising 15 or more consecutive nucleotides of the complement of a sequence selected from the group consisting of SEQ ID NO:1 (HOG3), SEQ ID NO:3 (HOG8), SEQ ID NO:5 (HOG18), SEQ ID NO:9 (CA9), SEQ ID NO:11 (HXB), SEQ ID NO:13 (IGFBP5), SEQ ID NO:15 (HFARP), SEQ ID NO:17(STC1), SEQ ID NO:19 (mig-6) and SEQ ID NO:21 (SSR4), whereby angiogenesis is inhibited.

2. The method of claim 1 wherein the antisense polynucleotide is provided by administering an expression vector with expresses said antisense polynucleotide.

3. The method of claim 1 wherein the antisense polynucleotide is administered to the subject.

4. A method of inhibiting angiogenesis associated with wound healing, retinopathy, ischemia, inflammation, microvasculopathy, bone healing, skin inflammation, or follicular development, comprising:

administering to a subject in need thereof an antibody which specifically binds to a polypeptide selected from the group consisting of SEQ ID NO:2 (HOG3), SEQ ID NO:4 (HOG8), SEQ ID NO:6 (HOG18), SEQ ID NO:10 (CA9), SEQ ID NO:12 (HXB), SEQ ID NO:14 (IGFBP5), SEQ ID NO:16 (HFARP), SEQ ID NO:18 (STC1), SEQ ID NO:20 (mig-6) and SEQ ID NO:22 (SSR4), whereby angiogenesis is inhibited.

5. The method of claim 4 wherein the antibody is a human antibody.

6. The method of claim 4 wherein the antibody is a humanized antibody.

7. The method of claim 4 wherein the antibody is a chimeric antibody.

8. The method of claim 4 wherein the antibody is an antigen-binding fragment of an antibody.

9. The method of claim 8 wherein the antigen-binding fragment is a single-chain Fv fragment.

10. A method of promoting angiogenesis associated with wound healing, retinopathy, ischemia, inflammation, microvasculopathy, bone healing, skin inflammation, or follicular development, comprising:

administering to a subject in need thereof a polypeptide selected from the group consisting of SEQ ID NO:2 (HOG3), SEQ ID NO:4 (HOG8), SEQ ID NO:6 (HOG18), SEQ ID NO:10 (CA9), SEQ ID NO:12 (HXB), SEQ ID NO:14 (IGFBP5), SEQ ID NO:16 (HFARP), SEQ ID NO:18 (STC1), SEQ ID NO:20 (mig-6) and SEQ ID NO:22 (SSR4), whereby angiogenesis is promoted.

11. A method of promoting angiogenesis associated with wound healing, retinopathy, ischemia, inflammation, microvasculopathy, bone healing, skin inflammation, or follicular development, comprising:

administering to a subject in need thereof a vector comprising a nucleotide sequence encoding a polypeptide selected from the group consisting of SEQ ID NO:2 (HOG3), SEQ ID NO:4 (HOG8), SEQ ID NO:6 (HOG18), SEQ ID NO:10 (CA9), SEQ ID NO:12 (HXB), SEQ ID NO:14 (IGFBP5), SEQ ID NO:16 (HFARP), SEQ ID NO:18 (STC1), SEQ ID NO:20 (mig-6) and SEQ ID NO:22 (SSR4) and a promotor, wherein the nucleotide sequence is operably linked to the promoter and is transcribed into a sense mRNA encoding said polypeptide upon transcription of the nucleotide sequence, whereby angiogenesis is promoted.

12. A method of treating a tumor, comprising:

providing to a subject in need thereof an antisense polynucleotide comprising 15 or more consecutive nucleotides of the complement of a sequence selected from the group consisting of SEQ ID NO:1 (HOG3), SEQ ID NO:3 (HOG8), SEQ ID NO:5

(HOG18), SEQ ID NO:13 (IGFBP5), SEQ ID NO:15 (HFARP), SEQ ID NO:19 (mig-6) and SEQ ID NO:21 (SSR4), whereby the growth of the tumor is diminished.

13. The method of claim 12 wherein the antisense polynucleotide is provided by administering an expression vector which expresses said antisense polynucleotide.

14. The method of claim 12 wherein the antisense polynucleotide is administered to the subject.

15. A method of treating a tumor, comprising:

administering to a subject in need thereof an antibody which specifically binds to a polypeptide selected from the group consisting of SEQ ID NO:2 (HOG3), SEQ ID NO:4 (HOG8), SEQ ID NO:6 (HOG18), SEQ ID NO:14 (IGFBP5), SEQ ID NO:16 (HFARP), SEQ ID NO:20 (mig-6) and SEQ ID NO:22 (SSR4), whereby the growth of the tumor is diminished.

16. The method of claim 15 wherein the antibody is a human antibody.

17. The method of claim 15 wherein the antibody is a humanized antibody.

18. The method of claim 15 wherein the antibody is a chimeric antibody.

19. The method of claim 15 wherein the antibody is an antigen-binding fragment.

20. The method of claim 19 wherein the antigen-binding fragment is a single-chain Fv fragment.

21. The method of claim 15 wherein the antibody is covalently linked to a chemotherapeutic anti-tumor agent or a radiotherapeutic anti-tumor agent.

22. A method of diagnosing cancer in a subject, comprising:

quantifying a polypeptide selected from the group consisting of SEQ ID NO:2 (HOG3), SEQ ID NO:4 (HOG8), SEQ ID NO:6 (HOG18), SEQ ID NO:8 (PLOD2), SEQ

ID NO:14 (IGFBP5), SEQ ID NO:16 (HFARP), SEQ ID NO:20 (mig-6) and SEQ ID NO:22 (SSR4), in a test sample suspected of being neoplastic from the subject and in a non-neoplastic control sample;

comparing the quantity of the polypeptide in a test sample suspected of being neoplastic with the quantity of the polypeptide in a non-neoplastic control sample; and

identifying the test sample as cancerous if the quantity of the polypeptide is higher in the test sample than in the control sample.

23. The method of claim 22 wherein the cancer is selected from the group consisting of breast cancer, colon cancer, and lung cancer.

24. The method of claim 22 wherein the cancer is glioblastoma.

25. The method of claim 22 wherein the step of quantifying is performed using an immunoassay.

26. The method of claim 25 wherein the step of quantifying is performed using Western blot or immunohistochemical assay.

27. A method of diagnosing cancer in a subject, comprising:

quantifying an mRNA selected from the group consisting of SEQ ID NO:1 (HOG3), SEQ ID NO:3 (HOG8), SEQ ID NO:5 (HOG18), SEQ ID NO:7 (PLOD2), SEQ ID NO:13 (IGFBP5), SEQ ID NO:15 (HFARP), SEQ ID NO:19 (mig-6) and SEQ ID NO:21 (SSR4), in a test sample suspected of being neoplastic from the subject and in a non-neoplastic control sample;

comparing the quantity of the mRNA in a test sample suspected of being neoplastic with the quantity of the mRNA in a non-neoplastic control sample; and

identifying the test sample as cancerous if the quantity of the mRNA is higher in the test sample than in the control sample.

28. The method of claim 27 wherein the step of quantifying employs a nucleic acid hybridization to a probe.

29. The method of claim 28 wherein the step of quantifying is performed using a Northern blot.

30. The method of claim 28 wherein the step of quantifying is performed using hybridization to probes in an array.

31. The method of claim 27 wherein mRNA is amplified before quantification.

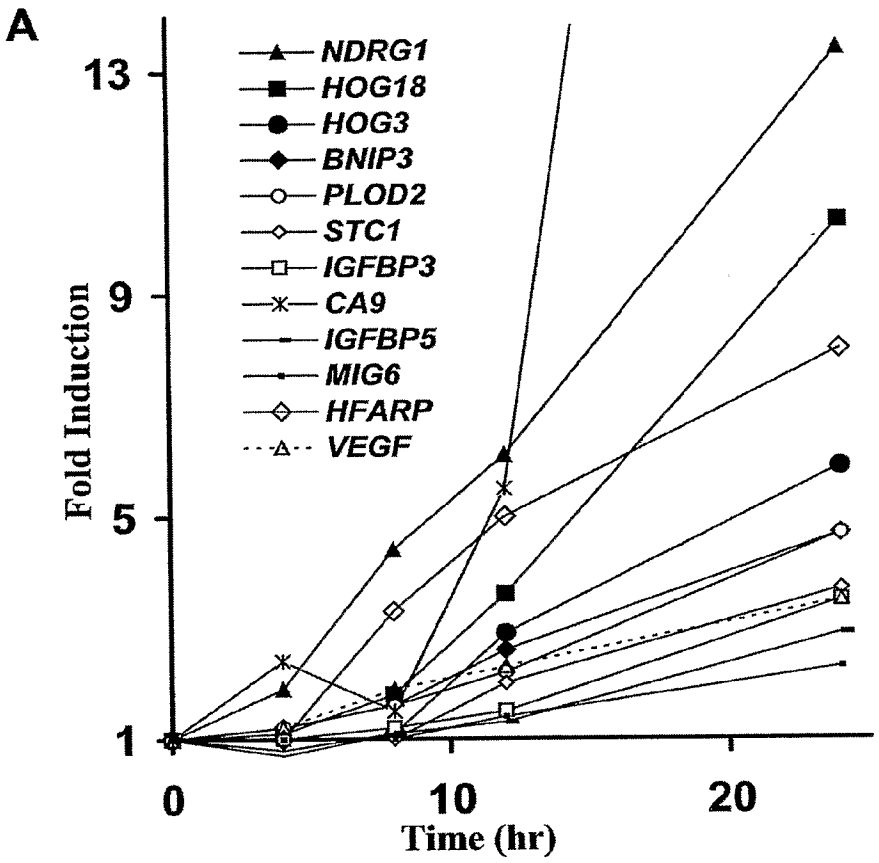
32. The method of claim 27 wherein the step of quantifying is performed using RT-PCR.

33. A method of imaging a tumor comprising:

administering to a subject or to a tissue sample from a subject an antibody which specifically binds to a polypeptide selected from the group consisting of SEQ ID NO:2 (HOG3), SEQ ID NO:4 (HOG8), SEQ ID NO:6 (HOG18), SEQ ID NO:8 (PLOD2), SEQ ID NO:14 (IGFBP5), SEQ ID NO:16 (HFARP), SEQ ID NO:20 (mig-6) and SEQ ID NO:22 (SSR4), wherein the antibody is covalently linked to a label; and

detecting the label, whereby an image is formed of the distribution of the label in the subject or tissue sample.

34. The method of claim 33 wherein the label is radioactive, fluorescent, or colored.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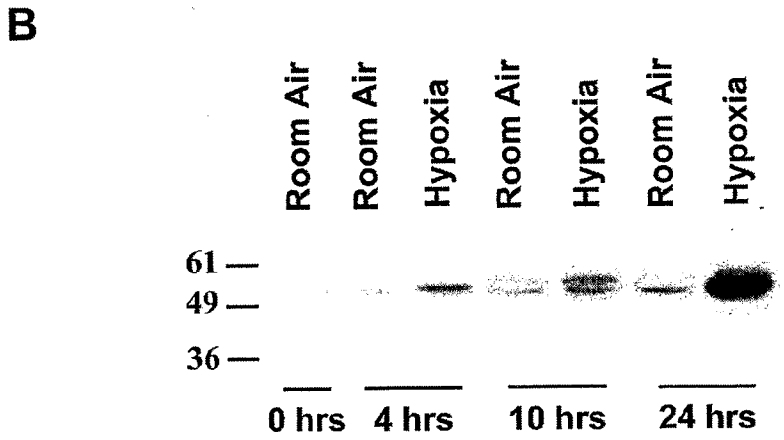
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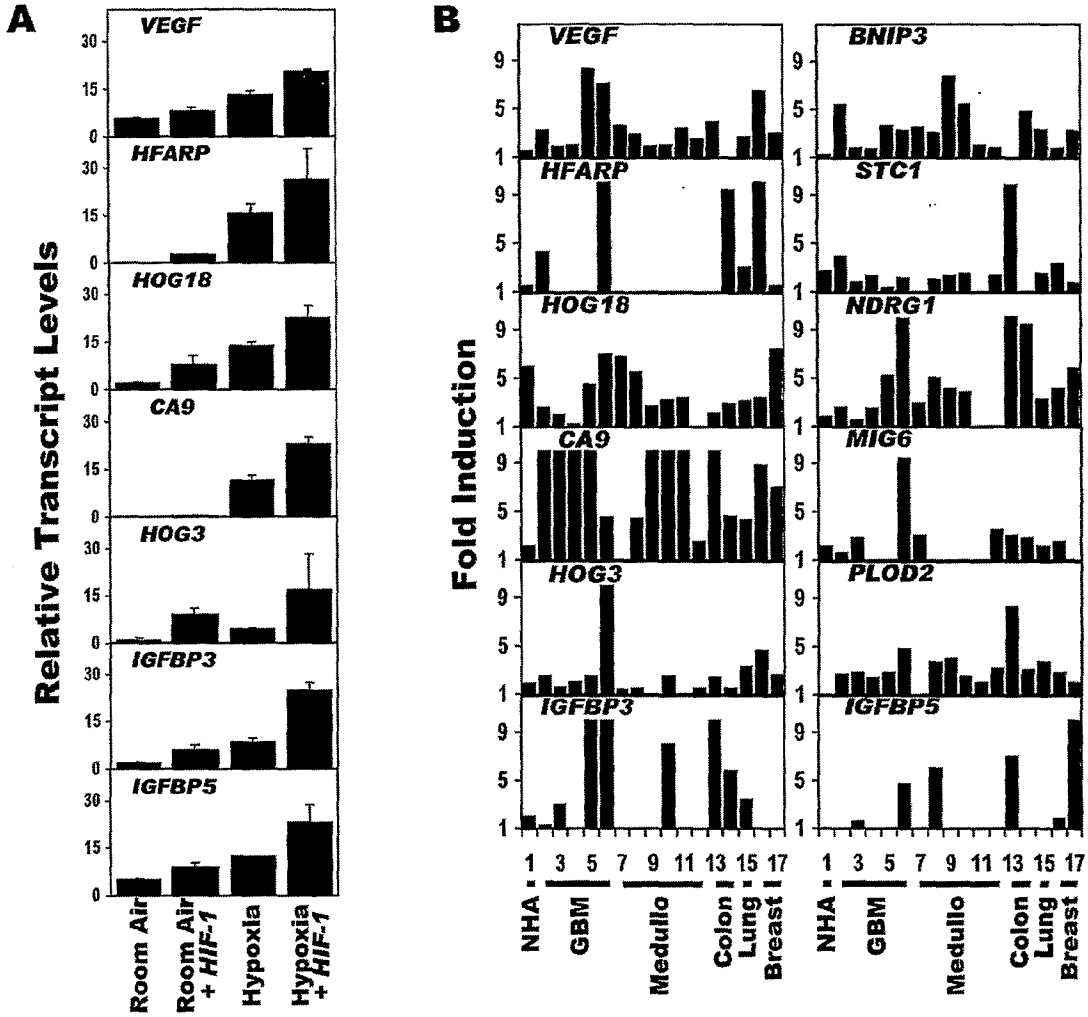
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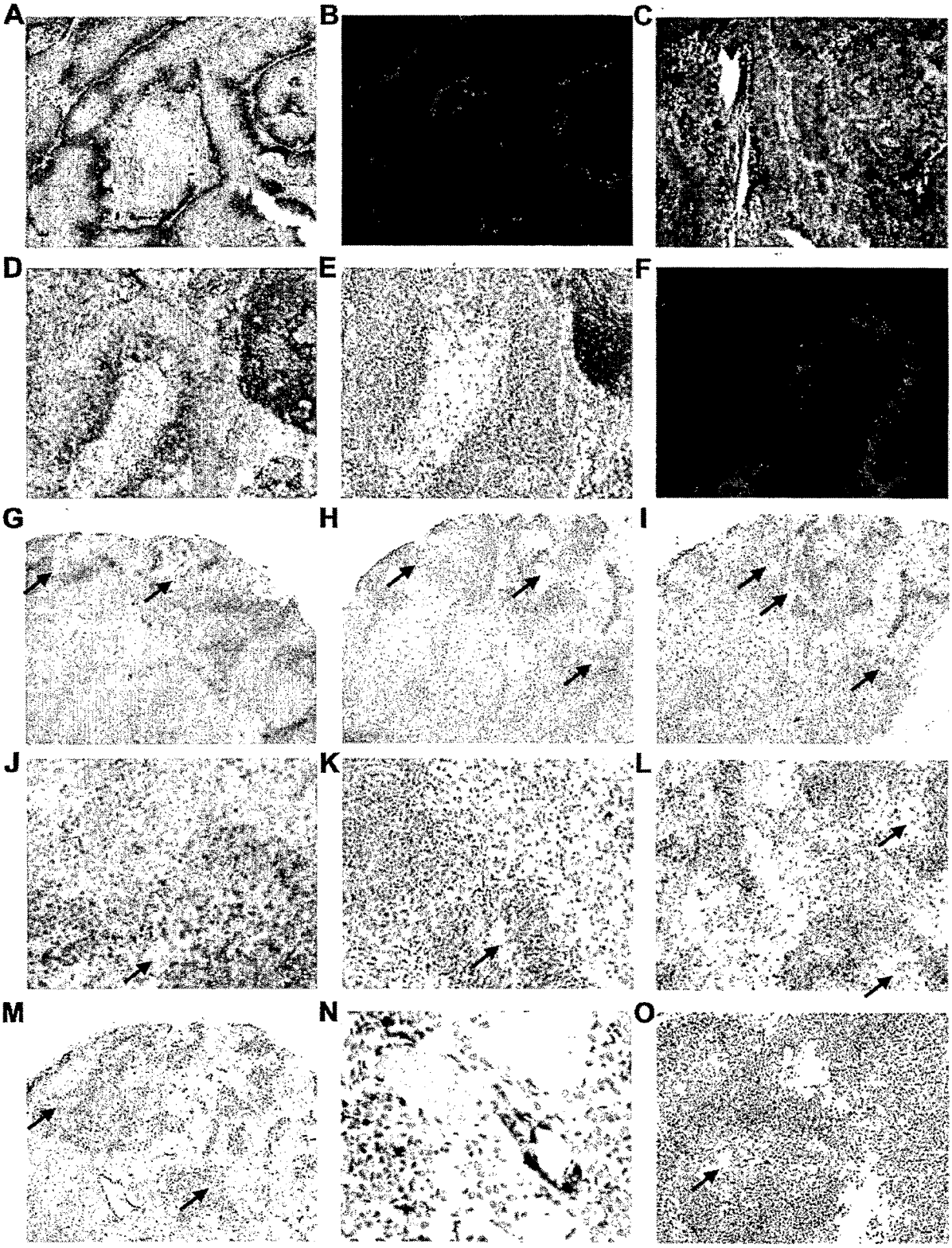
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<211> 737
<212> PRT
<213> Homo sapiens

<400> 8

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Ser Ile Pro Thr Asp Lys Leu Leu Val Ile Thr Val Ala Thr Lys Glu
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Ser Asp Gly Phe His Arg Phe Met Gln Ser Ala Lys Tyr Phe Asn Tyr
    50                  55                  60
Thr Val Lys Val Leu Gly Gln Gly Glu Glu Trp Arg Gly Gly Asp Gly
65                  70                  75                  80
Ile Asn Ser Ile Gly Gly Gly Gln Lys Val Arg Leu Met Lys Glu Val
                85                  90                  95
Met Glu His Tyr Ala Asp Gln Asp Asp Leu Val Val Met Phe Thr Glu
            100                 105                 110
Cys Phe Asp Val Ile Phe Ala Gly Gly Pro Glu Glu Val Leu Lys Lys
        115                 120                 125
Phe Gln Lys Ala Asn His Lys Val Val Phe Ala Ala Asp Gly Ile Leu
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Trp Pro Asp Lys Arg Leu Ala Asp Lys Tyr Pro Val Val His Ile Gly
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Lys Arg Tyr Leu Asn Ser Gly Gly Phe Ile Gly Tyr Ala Pro Tyr Val
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Asn Arg Ile Val Gln Gln Trp Asn Leu Gln Asp Asn Asp Asp Asp Gln
            180                 185                 190
Leu Phe Tyr Thr Lys Val Tyr Ile Asp Pro Leu Lys Arg Glu Ala Ile
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Asn Ile Thr Leu Asp His Lys Cys Lys Ile Phe Gln Thr Leu Asn Gly
    210                 215                 220
Ala Val Asp Glu Val Val Leu Lys Phe Glu Asn Gly Lys Ala Arg Ala
225                 230                 235                 240
Lys Asn Thr Phe Tyr Glu Thr Leu Pro Val Ala Ile Asn Gly Asn Gly
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Pro Thr Lys Ile Leu Leu Asn Tyr Phe Gly Asn Tyr Val Pro Asn Ser
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Trp Thr Gln Asp Asn Gly Cys Thr Leu Cys Glu Phe Asp Thr Val Asp
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305                 310                 315                 320
Leu Asp Tyr Pro Lys Glu Ala Leu Lys Leu Phe Ile His Asn Lys Glu
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Val Tyr His Glu Lys Asp Ile Lys Val Phe Phe Asp Lys Ala Lys His
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Glu Ile Lys Thr Ile Lys Ile Val Gly Pro Glu Glu Asn Leu Ser Gln
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Ala Glu Ala Arg Asn Met Gly Met Asp Phe Cys Arg Gln Asp Glu Lys
    370                 375                 380
Cys Asp Tyr Tyr Phe Ser Val Asp Ala Asp Val Val Leu Thr Asn Pro
385                 390                 395                 400
Arg Thr Leu Lys Ile Leu Ile Glu Gln Asn Arg Lys Ile Ile Ala Pro
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Leu Val Thr Arg His Gly Lys Leu Trp Ser Asn Phe Trp Gly Ala Leu
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Ser Pro Asp Gly Tyr Tyr Ala Arg Ser Glu Asp Tyr Val Asp Ile Val
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Gln Gly Asn Arg Val Gly Val Trp Asn Val Pro Tyr Met Ala Asn Val
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Tyr Leu Ile Lys Gly Lys Thr Leu Arg Ser Glu Met Asn Glu Arg Asn
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Ala Arg Glu Met Gly Val Phe Met Tyr Ile Ser Asn Arg His Glu Phe
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Gly Arg Leu Leu Ser Thr Ala Asn Tyr Asn Thr Ser His Tyr Asn Asn
        515                 520                 525
Asp Leu Trp Gln Ile Phe Glu Asn Pro Val Asp Trp Lys Glu Lys Tyr
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Ile Asn Arg Asp Tyr Ser Lys Ile Phe Thr Glu Asn Ile Val Glu Gln
545                 550                 555                 560
Pro Cys Pro Asp Val Phe Trp Phe Pro Ile Phe Ser Glu Lys Ala Cys
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Asp Glu Leu Val Glu Glu Met Glu His Tyr Gly Lys Trp Ser Gly Gly
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Lys His His Asp Ser Arg Ile Ser Gly Gly Tyr Glu Asn Val Pro Thr
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Asp Asp Ile His Met Lys Gln Val Asp Leu Glu Asn Val Trp Leu Asp
    610                 615                 620
Phe Ile Arg Glu Phe Ile Ala Pro Val Thr Leu Lys Val Phe Ala Gly
625                 630                 635                 640
Tyr Tyr Thr Lys Gly Phe Ala Leu Leu Asn Phe Val Val Lys Tyr Ser
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Pro Glu Arg Gln Arg Ser Leu Arg Pro His His Asp Ala Ser Thr Phe
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Thr Ile Asn Ile Ala Leu Asn Asn Val Gly Glu Asp Phe Gln Gly Gly
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Gly Cys Lys Phe Leu Arg Tyr Asn Cys Ser Ile Glu Ser Pro Arg Lys
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Gly Trp Ser Phe Met His Pro Gly Arg Leu Thr His Leu His Glu Gly
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<211> 1552
<212> DNA
<213> Homo sapiens

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<211> 459
<212> PRT
<213> Homo sapiens

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Met Pro Val His Pro Gln Arg Leu Pro Arg Met Gln Glu Asp Ser Pro
35 40 45
Leu Gly Gly Gly Ser Ser Gly Glu Asp Asp Pro Leu Gly Glu Glu Asp
50 55 60
Leu Pro Ser Glu Glu Asp Ser Pro Arg Glu Glu Asp Pro Pro Gly Glu
65 70 75 80
Glu Asp Leu Pro Gly Glu Glu Asp Leu Pro Gly Glu Glu Asp Leu Pro

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Glu Val Lys Pro Lys Ser Glu Glu Glu Gly Ser Leu Lys Leu Glu Asp
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Leu Pro Thr Val Glu Ala Pro Gly Asp Pro Gln Glu Pro Gln Asn Asn
        115                 120                 125
Ala His Arg Asp Lys Glu Gly Asp Asp Gln Ser His Trp Arg Tyr Gly
    130                 135                 140
Gly Asp Pro Pro Trp Pro Arg Val Ser Pro Ala Cys Ala Gly Arg Phe
145                 150                 155                 160
Gln Ser Pro Val Asp Ile Arg Pro Gln Leu Ala Ala Phe Cys Pro Ala
                165                 170                 175
Leu Arg Pro Leu Glu Leu Leu Gly Phe Gln Leu Pro Pro Leu Pro Glu
            180                 185                 190
Leu Arg Leu Arg Asn Asn Gly His Ser Val Gln Leu Thr Leu Pro Pro
        195                 200                 205
Gly Leu Glu Met Ala Leu Gly Pro Gly Arg Glu Tyr Arg Ala Leu Gln
    210                 215                 220
Leu His Leu His Trp Gly Ala Ala Gly Arg Pro Gly Ser Glu His Thr
225                 230                 235                 240
Val Glu Gly His Arg Phe Pro Ala Glu Ile His Val Val His Leu Ser
                245                 250                 255
Thr Ala Phe Ala Arg Val Asp Glu Ala Leu Gly Arg Pro Gly Gly Leu
            260                 265                 270
Ala Val Leu Ala Ala Phe Leu Glu Glu Gly Pro Glu Glu Asn Ser Ala
        275                 280                 285
Tyr Glu Gln Leu Leu Ser Arg Leu Glu Glu Ile Ala Glu Glu Gly Ser
    290                 295                 300
Glu Thr Gln Val Pro Gly Leu Asp Ile Ser Ala Leu Leu Pro Ser Asp
305                 310                 315                 320
Phe Ser Arg Tyr Phe Gln Tyr Glu Gly Ser Leu Thr Thr Pro Pro Cys
                325                 330                 335
Ala Gln Gly Val Ile Trp Thr Val Phe Asn Gln Thr Val Met Leu Ser
            340                 345                 350
Ala Lys Gln Leu His Thr Leu Ser Asp Thr Leu Trp Gly Pro Gly Asp
        355                 360                 365
Ser Arg Leu Gln Leu Asn Phe Arg Ala Thr Gln Pro Leu Asn Gly Arg
    370                 375                 380
Val Ile Glu Ala Ser Phe Pro Ala Gly Val Asp Ser Ser Pro Arg Ala
385                 390                 395                 400
Ala Glu Pro Val Gln Leu Asn Ser Cys Leu Ala Ala Gly Asp Ile Leu
                405                 410                 415
Ala Leu Val Phe Gly Leu Leu Phe Ala Val Thr Ser Val Ala Phe Leu
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<211> 7560
<212> DNA
<213> Homo sapiens

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<210> 12
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<212> PRT
<213> Homo sapiens

<400> 12

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        35                  40                  45
Val Phe Asn His Val Tyr Asn Ile Lys Leu Pro Val Gly Ser Gln Cys
    50                  55                  60
Ser Val Asp Leu Glu Ser Ala Ser Gly Glu Lys Asp Leu Ala Pro Pro
65                  70                  75                  80
Ser Glu Pro Ser Glu Ser Phe Gln Glu His Thr Val Asp Gly Glu Asn
                85                  90                  95
Gln Ile Val Phe Thr His Arg Ile Asn Ile Pro Arg Arg Ala Cys Gly
            100                 105                 110
Cys Ala Ala Ala Pro Asp Val Lys Glu Leu Leu Ser Arg Leu Glu Glu
        115                 120                 125
Leu Glu Asn Leu Val Ser Ser Leu Arg Glu Gln Cys Thr Ala Gly Ala
    130                 135                 140
Gly Cys Cys Leu Gln Pro Ala Thr Gly Arg Leu Asp Thr Arg Pro Phe
145                 150                 155                 160
Cys Ser Gly Arg Gly Asn Phe Ser Thr Glu Gly Cys Gly Cys Val Cys
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Glu Pro Gly Trp Lys Gly Pro Asn Cys Ser Glu Pro Glu Cys Pro Gly
            180                 185                 190
Asn Cys His Leu Arg Gly Arg Cys Ile Asp Gly Gln Cys Ile Cys Asp
        195                 200                 205
Asp Gly Phe Thr Gly Glu Asp Cys Ser Gln Leu Ala Cys Pro Ser Asp
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Cys Asn Asp Gln Gly Lys Cys Val Asn Gly Val Cys Ile Cys Phe Glu
225                 230                 235                 240
Gly Tyr Ala Gly Ala Asp Cys Ser Arg Glu Ile Cys Pro Val Pro Cys
                245                 250                 255
Ser Glu Glu His Gly Thr Cys Val Asp Gly Leu Cys Val Cys His Asp
            260                 265                 270
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Tyr Asn Arg Gly Arg Cys Val Glu Asn Glu Cys Val Cys Asp Glu Gly
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Phe Thr Gly Glu Asp Cys Ser Glu Leu Ile Cys Pro Asn Asp Cys Phe
305                 310                 315                 320
Asp Arg Gly Arg Cys Ile Asn Gly Thr Cys Tyr Cys Glu Glu Gly Phe
                325                 330                 335
Thr Gly Glu Asp Cys Gly Lys Pro Thr Cys Pro His Ala Cys His Thr
            340                 345                 350
Gln Gly Arg Cys Glu Glu Gly Gln Cys Val Cys Asp Glu Gly Phe Ala
        355                 360                 365
Gly Leu Asp Cys Ser Glu Lys Arg Cys Pro Ala Asp Cys His Asn Arg
    370                 375                 380
Gly Arg Cys Val Asp Gly Arg Cys Glu Cys Asp Asp Gly Phe Thr Gly
385                 390                 395                 400
Ala Asp Cys Gly Glu Leu Lys Cys Pro Asn Gly Cys Ser Gly His Gly
                405                 410                 415
Arg Cys Val Asn Gly Gln Cys Val Cys Asp Glu Gly Tyr Thr Gly Glu
            420                 425                 430
Asp Cys Ser Gln Leu Arg Cys Pro Asn Asp Cys His Ser Arg Gly Arg
        435                 440                 445
Cys Val Glu Gly Lys Cys Val Cys Glu Gln Gly Phe Lys Gly Tyr Asp
    450                 455                 460
Cys Ser Asp Met Ser Cys Pro Asn Asp Cys His Gln His Gly Arg Cys
465                 470                 475                 480
Val Asn Gly Met Cys Val Cys Asp Asp Gly Tyr Thr Gly Glu Asp Cys
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Arg Asp Arg Gln Cys Pro Arg Asp Cys Ser Asn Arg Gly Leu Cys Val
            500                 505                 510
Asp Gly Gln Cys Val Cys Glu Asp Gly Phe Thr Gly Pro Asp Cys Ala
        515                 520                 525
Glu Leu Ser Cys Pro Asn Asp Cys His Gly Gln Gly Arg Cys Val Asn
    530                 535                 540
Gly Gln Cys Val Cys His Glu Gly Phe Met Gly Lys Asp Cys Lys Glu
545                 550                 555                 560
Gln Arg Cys Pro Ser Asp Cys His Gly Gln Gly Arg Cys Val Asp Gly
                565                 570                 575
Gln Cys Ile Cys His Glu Gly Phe Thr Gly Leu Asp Cys Gly Gln His
            580                 585                 590
Ser Cys Pro Ser Asp Cys Asn Asn Leu Gly Gln Cys Val Ser Gly Arg
        595                 600                 605
Cys Ile Cys Asn Glu Gly Tyr Ser Gly Glu Asp Cys Ser Glu Val Ser
    610                 615                 620
Pro Pro Lys Asp Leu Val Val Thr Glu Val Thr Glu Glu Thr Val Asn
625                 630                 635                 640
Leu Ala Trp Asp Asn Glu Met Arg Val Thr Glu Tyr Leu Val Val Tyr
                645                 650                 655
Thr Pro Thr His Glu Gly Gly Leu Glu Met Gln Phe Arg Val Pro Gly
            660                 665                 670
Asp Gln Thr Ser Thr Ile Ile Gln Glu Leu Glu Pro Gly Val Glu Tyr
        675                 680                 685
Phe Ile Arg Val Phe Ala Ile Leu Glu Asn Lys Lys Ser Ile Pro Val
    690                 695                 700
Ser Ala Arg Val Ala Thr Tyr Leu Pro Ala Pro Glu Gly Leu Lys Phe
705                 710                 715                 720
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Lys Ser Ile Lys Glu Thr Ser Val Glu Val Glu Trp Asp Pro Leu Asp
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Ile Ala Phe Glu Thr Trp Glu Ile Ile Phe Arg Asn Met Asn Lys Glu
            740                 745                 750
Asp Glu Gly Glu Ile Thr Lys Ser Leu Arg Arg Pro Glu Thr Ser Tyr
        755                 760                 765
Arg Gln Thr Gly Leu Ala Pro Gly Gln Glu Tyr Glu Ile Ser Leu His
    770                 775                 780
Ile Val Lys Asn Asn Thr Arg Gly Pro Gly Leu Lys Arg Val Thr Thr
785                 790                 795                 800
Thr Arg Leu Asp Ala Pro Ser Gln Ile Glu Val Lys Asp Val Thr Asp
                805                 810                 815
Thr Thr Ala Leu Ile Thr Trp Phe Lys Pro Leu Ala Glu Ile Asp Gly
            820                 825                 830
Ile Glu Leu Thr Tyr Gly Ile Lys Asp Val Pro Gly Asp Arg Thr Thr
        835                 840                 845
Ile Asp Leu Thr Glu Asp Glu Asn Gln Tyr Ser Ile Gly Asn Leu Lys
    850                 855                 860
Pro Asp Thr Glu Tyr Glu Val Ser Leu Ile Ser Arg Arg Gly Asp Met
865                 870                 875                 880
Ser Ser Asn Pro Ala Lys Glu Thr Phe Thr Thr Gly Leu Asp Ala Pro
                885                 890                 895
Arg Asn Leu Arg Arg Val Ser Gln Thr Asp Asn Ser Ile Thr Leu Glu
            900                 905                 910
Trp Arg Asn Gly Lys Ala Ala Ile Asp Ser Tyr Arg Ile Lys Tyr Ala
        915                 920                 925
Pro Ile Ser Gly Gly Asp His Ala Glu Val Asp Val Pro Lys Ser Gln
    930                 935                 940
Gln Ala Thr Thr Lys Thr Thr Leu Thr Gly Leu Arg Pro Gly Thr Glu
945                 950                 955                 960
Tyr Gly Ile Gly Val Ser Ala Val Lys Glu Asp Lys Glu Ser Asn Pro
                965                 970                 975
Ala Thr Ile Asn Ala Ala Thr Glu Leu Asp Thr Pro Lys Asp Leu Gln
            980                 985                 990
Val Ser Glu Thr Ala Glu Thr Ser Leu Thr Leu Leu Trp Lys Thr Pro
        995                 1000                1005
Leu Ala Lys Phe Asp Arg Tyr Arg Leu Asn Tyr Ser Leu Pro Thr Gly
    1010                1015                1020
Gln Trp Val Gly Val Gln Leu Pro Arg Asn Thr Thr Ser Tyr Val Leu
1025                1030                1035                1040
Arg Gly Leu Glu Pro Gly Gln Glu Tyr Asn Val Leu Leu Thr Ala Glu
                1045                1050                1055
Lys Gly Arg His Lys Ser Lys Pro Ala Arg Val Lys Ala Ser Thr Glu
            1060                1065                1070
Gln Ala Pro Glu Leu Glu Asn Leu Thr Val Thr Glu Val Gly Trp Asp
        1075                1080                1085
Gly Leu Arg Leu Asn Trp Thr Ala Ala Asp Gln Ala Tyr Glu His Phe
    1090                1095                1100
Ile Ile Gln Val Gln Glu Ala Asn Lys Val Glu Ala Ala Arg Asn Leu
1105                1110                1115                1120
Thr Val Pro Gly Ser Leu Arg Ala Val Asp Ile Pro Gly Leu Lys Ala
                1125                1130                1135
Ala Thr Pro Tyr Thr Val Ser Ile Tyr Gly Val Ile Gln Gly Tyr Arg
            1140                1145                1150
Thr Pro Val Leu Ser Ala Glu Ala Ser Thr Gly Glu Thr Pro Asn Leu
        1155                1160                1165
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Gly Glu Val Val Val Ala Glu Val Gly Trp Asp Ala Leu Lys Leu Asn
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Trp Thr Ala Pro Glu Gly Ala Tyr Glu Tyr Phe Phe Ile Gln Val Gln
1185                1190                1195                1200
Glu Ala Asp Thr Val Glu Ala Ala Gln Asn Leu Thr Val Pro Gly Gly
                1205                1210                1215
Leu Arg Ser Thr Asp Leu Pro Gly Leu Lys Ala Ala Thr His Tyr Thr
            1220                1225                1230
Ile Thr Ile Arg Gly Val Thr Gln Asp Phe Ser Thr Thr Pro Leu Ser
        1235                1240                1245
Val Glu Val Leu Thr Glu Glu Val Pro Asp Met Gly Asn Leu Thr Val
    1250                1255                1260
Thr Glu Val Ser Trp Asp Ala Leu Arg Leu Asn Trp Thr Thr Pro Asp
1265                1270                1275                1280
Gly Thr Tyr Asp Gln Phe Thr Ile Gln Val Gln Glu Ala Asp Gln Val
                1285                1290                1295
Glu Glu Ala His Asn Leu Thr Val Pro Gly Ser Leu Arg Ser Met Glu
            1300                1305                1310
Ile Pro Gly Leu Arg Ala Gly Thr Pro Tyr Thr Val Thr Leu His Gly
        1315                1320                1325
Glu Val Arg Gly His Ser Thr Arg Pro Leu Ala Val Glu Val Val Thr
    1330                1335                1340
Glu Asp Leu Pro Gln Leu Gly Asp Leu Ala Val Ser Glu Val Gly Trp
1345                1350                1355                1360
Asp Gly Leu Arg Leu Asn Trp Thr Ala Ala Asp Asn Ala Tyr Glu His
                1365                1370                1375
Phe Val Ile Gln Val Gln Glu Val Asn Lys Val Glu Ala Ala Gln Asn
            1380                1385                1390
Leu Thr Leu Pro Gly Ser Leu Arg Ala Val Asp Ile Pro Gly Leu Glu
        1395                1400                1405
Ala Ala Thr Pro Tyr Arg Val Ser Ile Tyr Gly Val Ile Arg Gly Tyr
    1410                1415                1420
Arg Thr Pro Val Leu Ser Ala Glu Ala Ser Thr Ala Lys Glu Pro Glu
1425                1430                1435                1440
Ile Gly Asn Leu Asn Val Ser Asp Ile Thr Pro Glu Ser Phe Asn Leu
                1445                1450                1455
Ser Trp Met Ala Thr Asp Gly Ile Phe Glu Thr Phe Thr Ile Glu Ile
            1460                1465                1470
Ile Asp Ser Asn Arg Leu Leu Glu Thr Val Glu Tyr Asn Ile Ser Gly
        1475                1480                1485
Ala Glu Arg Thr Ala His Ile Ser Gly Leu Pro Pro Ser Thr Asp Phe
    1490                1495                1500
Ile Val Tyr Leu Ser Gly Leu Ala Pro Ser Ile Arg Thr Lys Thr Ile
1505                1510                1515                1520
Ser Ala Thr Ala Thr Thr Glu Ala Leu Pro Leu Leu Glu Asn Leu Thr
                1525                1530                1535
Ile Ser Asp Ile Asn Pro Tyr Gly Phe Thr Val Ser Trp Met Ala Ser
            1540                1545                1550
Glu Asn Ala Phe Asp Ser Phe Leu Val Thr Val Val Asp Ser Gly Lys
        1555                1560                1565
Leu Leu Asp Pro Gln Glu Phe Thr Leu Ser Gly Thr Gln Arg Lys Leu
    1570                1575                1580
Glu Leu Arg Gly Leu Ile Thr Gly Ile Gly Tyr Glu Val Met Val Ser
1585                1590                1595                1600
Gly Phe Thr Gln Gly His Gln Thr Lys Pro Leu Arg Ala Glu Ile Val
                1605                1610                1615
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Thr Glu Ala Glu Pro Glu Val Asp Asn Leu Leu Val Ser Asp Ala Thr
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Pro Asp Gly Phe Arg Leu Ser Trp Thr Ala Asp Glu Gly Val Phe Asp
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Asn Phe Val Leu Lys Ile Arg Asp Thr Lys Lys Gln Ser Glu Pro Leu
    1650                1655                1660
Glu Ile Thr Leu Leu Ala Pro Glu Arg Thr Arg Asp Leu Thr Gly Leu
1665                1670                1675                1680
Arg Glu Ala Thr Glu Tyr Glu Ile Glu Leu Tyr Gly Ile Ser Lys Gly
                1685                1690                1695
Arg Arg Ser Gln Thr Val Ser Ala Ile Ala Thr Thr Ala Met Gly Ser
            1700                1705                1710
Pro Lys Glu Val Ile Phe Ser Asp Ile Thr Glu Asn Ser Ala Thr Val
        1715                1720                1725
Ser Trp Arg Ala Pro Thr Ala Gln Val Glu Ser Phe Arg Ile Thr Tyr
    1730                1735                1740
Val Pro Ile Thr Gly Gly Thr Pro Ser Met Val Thr Val Asp Gly Thr
1745                1750                1755                1760
Lys Thr Gln Thr Arg Leu Val Lys Leu Ile Pro Gly Val Glu Tyr Leu
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Val Ser Ile Ile Ala Met Lys Gly Phe Glu Glu Ser Glu Pro Val Ser
            1780                1785                1790
Gly Ser Phe Thr Thr Ala Leu Asp Gly Pro Ser Gly Leu Val Thr Ala
        1795                1800                1805
Asn Ile Thr Asp Ser Glu Ala Leu Ala Arg Trp Gln Pro Ala Ile Ala
    1810                1815                1820
Thr Val Asp Ser Tyr Val Ile Ser Tyr Thr Gly Glu Lys Val Pro Glu
1825                1830                1835                1840
Ile Thr Arg Thr Val Ser Gly Asn Thr Val Glu Tyr Ala Leu Thr Asp
                1845                1850                1855
Leu Glu Pro Ala Thr Glu Tyr Thr Leu Arg Ile Phe Ala Glu Lys Gly
            1860                1865                1870
Pro Gln Lys Ser Ser Thr Ile Thr Ala Lys Phe Thr Thr Asp Leu Asp
        1875                1880                1885
Ser Pro Arg Asp Leu Thr Ala Thr Glu Val Gln Ser Glu Thr Ala Leu
    1890                1895                1900
Leu Thr Trp Arg Pro Pro Arg Ala Ser Val Thr Gly Tyr Leu Leu Val
1905                1910                1915                1920
Tyr Glu Ser Val Asp Gly Thr Val Lys Glu Val Ile Val Gly Pro Asp
                1925                1930                1935
Thr Thr Ser Tyr Ser Leu Ala Asp Leu Ser Pro Ser Thr His Tyr Thr
            1940                1945                1950
Ala Lys Ile Gln Ala Leu Asn Gly Pro Leu Arg Ser Asn Met Ile Gln
        1955                1960                1965
Thr Ile Phe Thr Thr Ile Gly Leu Leu Tyr Pro Phe Pro Lys Asp Cys
    1970                1975                1980
Ser Gln Ala Met Leu Asn Gly Asp Thr Thr Ser Gly Leu Tyr Thr Ile
1985                1990                1995                2000
Tyr Leu Asn Gly Asp Lys Ala Gln Ala Leu Glu Val Phe Cys Asp Met
                2005                2010                2015
Thr Ser Asp Gly Gly Gly Trp Ile Val Phe Leu Arg Arg Lys Asn Gly
            2020                2025                2030
Arg Glu Asn Phe Tyr Gln Asn Trp Lys Ala Tyr Ala Ala Gly Phe Gly
        2035                2040                2045
Asp Arg Arg Glu Glu Phe Trp Leu Gly Leu Asp Asn Leu Asn Lys Ile
    2050                2055                2060
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Thr Ala Gln Gly Gln Tyr Glu Leu Arg Val Asp Leu Arg Asp His Gly
2065                2070                2075                2080
Glu Thr Ala Phe Ala Val Tyr Asp Lys Phe Ser Val Gly Asp Ala Lys
                2085                2090                2095
Thr Arg Tyr Lys Leu Lys Val Glu Gly Tyr Ser Gly Thr Ala Gly Asp
            2100                2105                2110
Ser Met Ala Tyr His Asn Gly Arg Ser Phe Ser Thr Phe Asp Lys Asp
        2115                2120                2125
Thr Asp Ser Ala Ile Thr Asn Cys Ala Leu Ser Tyr Lys Gly Ala Phe
    2130                2135                2140
Trp Tyr Arg Asn Cys His Arg Val Asn Leu Met Gly Arg Tyr Gly Asp
2145                2150                2155                2160
Asn Asn His Ser Gln Gly Val Asn Trp Phe His Trp Lys Gly His Glu
                2165                2170                2175
His Ser Ile Gln Phe Ala Glu Met Lys Leu Arg Pro Ser Asn Phe Arg
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Asn Leu Glu Gly Arg Arg Lys Arg Ala
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<210> 13
<211> 3672
<212> DNA
<213> Homo sapiens

<400> 13

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<210> 14
<211> 272
<212> PRT
<213> Homo sapiens

<400> 14

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            20                  25                  30
Lys Ala Leu Ser Met Cys Pro Pro Ser Pro Leu Gly Cys Glu Leu Val
        35                  40                  45
Lys Glu Pro Gly Cys Gly Cys Cys Met Thr Cys Ala Leu Ala Glu Gly
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Cys Asp Thr Asp Gly Met Tyr Asp Ile Cys Lys Ser Phe Leu Tyr Ser
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Ala Ala Lys Phe Asp Thr Gln Gly Lys Ala Phe Val Lys Glu Ser Leu
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Ala Asp Phe Asn Arg Arg Arg Thr Asn Glu Pro Gln Lys Leu Lys Val
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Gln Ser Phe Ala Pro Asp Pro Lys Tyr Val Ser Ser Lys Ala Leu Gln

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            100                 105                 110
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65                  70                  75                  80
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Ser Leu Leu Arg Lys Ala Gln Arg Asn Asn Glu Asp Ile Ser Ile Ile
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/23786

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07K 21/04, 16/00; A61K 48/00, 39/395; C12N 15/00

US CL : 435/6, 7.1, 375, 377; 536, 24.5; 424/130.1; 514/2, 44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 7.1, 375, 377; 536, 24.5; 424/130.1; 514/2, 44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, MEDLINE, BIOSIS, SCISEARCH, EMBASE, CAPLUS, BIOTECHNO

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,E	US 2002/0103353 A1 (EINAT et al.) 01 August 2002, see entire document	1-34
Y	US 6,008,322 A (KUESTNER et al.) 28 December 1999, see entire document.	1-34
A,P	US 2002/0009739 A1 (GIESE) 24 January 2002, see entire document.	1-34
Y	ROZEN et al. Inhibition of Insulin-Like Growth Factor I Receptor Signaling by the Vitamin D Analogue EB1089 in MCF-7 Breast Cancer Cells: A Role for Insulin-Like Factor Binding Proteins. International Journal of Oncology. 1999, Vol. 15, pages 589-594, see entire document.	1-34
Y	FAUST et al. Antisense Oligonucleotides Against Protein Kinase CK2-alpha Inhibit Growth of Squamous Cell Carcinoma of the Head and Neck in vitro. Head and Neck. July 2000, Vol. 22,No. 4, pages 341-346, see entire document.	1-34

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

17 October 2002 (17.10.2002)

Date of mailing of the international search report

18 DEC 2002

Name and mailing address of the ISA/US

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Form PCT/ISA/210 (second sheet) (July 1998)